Unraveling the 'chemobrain'

Pullens, M.J.J.

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About the author: Marleen Pullens was born on April 25, 1985 in Tilburg, the Netherlands. After she completed her pre-university education at Cobbenhagen College in Tilburg in 2003, she obtained her Bachelor's degree in Health Psychology at Tilburg University in 2006. Subsequently, she completed the two-year Master Medical Psychology with a specialization in Neuropsychology at the same institution in August 2008. She did her clinical internship at the department of Medical Psychology of the TweeSteden hospital in Tilburg. Her research internship focused on risk factors for delirium in geriatric patients and on cognitive and functional outcomes. Furthermore, she assisted in a research focused on sexual functioning and quality of life in women after pelvic surgery. Thereafter, she started her PhD project at Tilburg University in September 2008. This dissertation is presenting this research, which is focussing on cognitive functioning and quality of life in patients with breast cancer who are treated with chemotherapy. This study was financed by the Dutch Cancer Society and was supervised by prof. dr. Jolanda De Vries and prof. dr. Jan A. Roukema. In all these years she has been engaged in several extracurricular activities as for instance a member of the PhD-council, a voluntary worker and a faculty representative at information meetings. Since December 2012 she is working as a teacher at HAN University of Applied Sciences (Hogeschool Arnhem en Nijmegen) for the Master Advanced Nursing Practice.

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A prospective study in patients with breast cancer

Marleen J.J. Pullens

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Uitnodiging

voor het bijwonen van
de openbare verdediging
van mijn proefschrift

Unraveling the 'chemobrain'

A prospective study in patients with breast cancer

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Aansluitend is er een
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Marleen Pullens
Theresiaplein 21
5041 BJ Tilburg
mjjpullens@gmail.com
06-47691830

Paranimfen
Kim Klaassen

Marjan Traa

Hester Duivis
h.e.duivis@tilburguniversity.edu
06-22850812

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Marleen Jantien Jozefien Pullens

geboren op 25 april 1985 te Tilburg

Promotores

Prof. dr. J. de Vries
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Promotiecommissie

Prof. dr. J. Denollet
Prof. dr. G.L.M. van Heck
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Voor

Paul en Maarten

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Chapter 1

Introduction

Worldwide, breast cancer (BC) is the most common type of cancer among women, accounting for 23% of the total number of cancer incidence [1]. In 2010 in the Netherlands, the ten-year prevalence of women with BC was 97266, with 13257 new cases of BC [2]. Due to advancements in treatment an increasing number of women live with the long-term effects of BC and its treatment [3]. BC treatment consists of primary loco-regional treatment (surgery), often in combination with adjuvant treatment. Adjuvant treatment is recommended depending on type of surgery, tumor size, degree of differentiation of the tumor, and the presence of axillary metastases. Chemotherapy, hormone therapy and radiotherapy can be recommended separately or in combination, based on national guidelines [4]. These days, 60% of the newly diagnosed BC patients younger than 65 years receive chemotherapy [5].

Breast cancer treatment and cognitive functioning

Although adjuvant chemotherapy significantly improves the clinical outcome of patients with early-stage BC, it is also known to have severe side-effects [3]. Apart from common complaints, such as fatigue, hair loss, and depression [6], cognitive impairment after chemotherapy, also known as 'chemobrain', is a reported concern of BC patients [7]. There is a growing body of research concerning the influence of adjuvant treatment on cognitive functioning in BC patients and survivors [7-41].

When investigating cognitive functioning, a distinction must be made between objective cognitive functioning (OCF), measured with standardized neuropsychological tests, and subjective cognitive functioning (SCF), measured with self-report questionnaires [21]. SCF refers to the *amount* of cognitive problems a person experiences in daily life and the *satisfaction* with cognitive functioning [42]. Whether chemotherapy influences OCF or SCF is still inconclusive and prevalence rates vary strongly. These inconclusive results may be due to inconsistencies in study designs as well as methods of analysis. Some studies did not include a control group (e.g., [26, 43, 44]). However, in studies in which a control group was included, groups varied from healthy controls (e.g., [14, 27, 28]), cardiac patients [27], or BC patients treated with hormone therapy or radiotherapy (e.g., [20, 45, 46]). Although all studies used neuropsychological tests to measure OCF, there is a large variation in the neuropsychological tests employed and in the definitions used to determine cognitive impairment. For instance, cognitive impairment was defined as one or two standard deviations below the mean of a specific test, and the number of impaired tests that is necessary to define the person as 'cognitive impaired' also varied between studies. Also, different reference data were used to classify patients as impaired or not. Furthermore, not all the longitudinal studies used a baseline measurement *before* chemotherapy was started (e.g., [44]), and timing of cognitive assessments varied between follow-up moments *during* chemotherapy (e.g., [26]) to measurements one year later (e.g., [9, 20, 28, 29, 43, 46] or even 20 years later [47]. Moreover, although most studies have controlled for a number of factors, there is also much variability in the assessed mediators and moderators of the relationship between chemotherapy and

cognitive functioning. The different age range of the included patients is another problem in the interpretation of the different existing studies. Maybe as a consequence of the wide variety in these aspects, no consistent findings have been reported with regard to the specific cognitive domain that is affected.

Due to the aforementioned heterogeneity, there is a need for more research [48]. The International Cognition and Cancer Task Force provided research recommendations and guidelines to increase the homogeneity of studies [49]. They recommend longitudinal studies with a pre-treatment assessment. Furthermore, a control group should be included who undergo the same cognitive assessments in the same timeframe as the BC group. This approach makes it also possible to deal with practice effect i.e., change in neuropsychological performance over time due to familiarity with a test instead of a true improvement. Another recommendation is to assess at least the following cognitive domains: learning and memory, processing speed and executive functioning.

Aim and clinical importance of the study

Until now, the prospective studies examining the effect of chemotherapy on cognitive functioning in BC patients are limited and methodologically heterogeneous. Therefore, the aim of the current thesis was to examine the effects of chemotherapy on cognitive functioning (SCF and OCF) and quality of life (QoL) in BC patients in a prospective multicenter study. The evaluation of the potential effects of chemotherapy on cognitive functioning in BC patients is of great importance since it is a frequently reported complain of BC patients in clinical practice. Information about the existence, prevalence and course of problems with cognitive functioning can facilitate health care professionals to provide evidence-based information to their patients. Furthermore, knowledge about predictors of problems with SCF and OCF can underpin health care professionals in noticing patients with a higher risk to develop problems with cognitive functioning after their BC treatment in an earlier stage. This creates the opportunity to provide specific information and possibly an intervention to the patients in an earlier stage in order to limit the concerns about the complaints of cognitive functioning. The derived knowledge may also be used for the development of intervention techniques for BC patients who suffer from SCF and/or OCF. Besides the understanding of cognitive deficits following cancer treatment, the functional significance of these deficits also has to be considered. Focusing on the relationship between neuropsychological decline secondary to chemotherapy and QoL will enable a better understanding of the relative impact of cognitive functioning on the well-being of BC patients. Relatively few studies have focused on the impact of problems in cognitive functioning due to chemotherapy on aspects of QoL. Thus, another aim of this thesis was to examine the clinical significance of cognitive changes in BC patients' lives.

Design of the study

Women who were diagnosed with early stage BC (tumor smaller than five cm in diameter and there are no apparent metastases beyond the axilla) and were about to receive chemotherapy in St. Elisabeth hospital (Tilburg), TweeSteden hospital (Tilburg), Máxima Medical Centre (Eindhoven, Veldhoven), Catharina hospital (Eindhoven), St. Anna hospital (Geldrop), Amphia hospital (Breda), and Jeroen Bosch hospital (Den Bosch) were eligible for this study. In addition, women diagnosed with a benign breast disease (BBD) were also asked to participate. A cyst, mastopathy or a fibro-adenoma are the most common BBD diagnoses. Treatment of the BBD is not necessary for most women but some women are invited for a follow-up examination three or six months later. Furthermore, some women want their cyst or fibro-adenoma surgically removed. Women with proven BC recurrence or distant metastases were excluded. Other exclusion criteria were: a history of neuropsychological and/or psychiatric signs or symptoms that lead to deviant neuropsychological test results (e.g., dementia), the use of medication that may lead to deviant neuropsychological results, alcohol and/or drug addiction, and a poor expression in the Dutch language. BC patients were assessed prior to initiation of adjuvant chemotherapy (Time 1), three months (Time 2) and one year (Time 3) following the last cycle of chemotherapy. Patients with a BBD were assessed at comparable time points (see Figure 1). All participants provided written informed consent. At each time point questionnaires were completed and patients underwent a neuropsychological assessment.

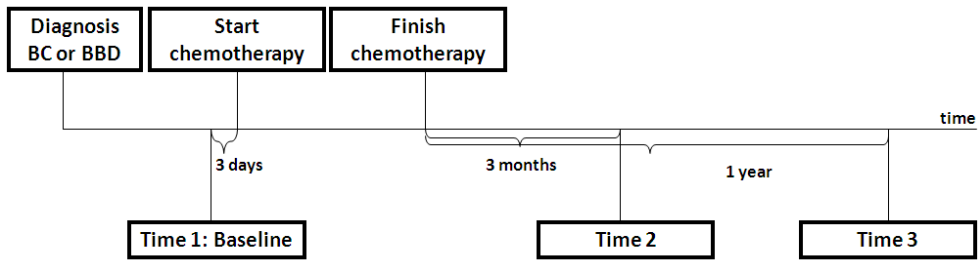

Figure 1: Timeline of the study
BC = Breast cancer; BBD = Benign breast disease

Neuropsychological assessment

A comprehensive test battery, which took approximately 1.5 hours to complete, was designed to assess a broad range of cognitive domains. The battery of 14 neuropsychological tests (comprising 24 test indexes) covered attention/processing speed, verbal and visual memory, visuospatial functioning, verbal fluency, executive functioning and motor functioning. In addition, the Dutch Adult Reading test provides information on verbal premorbid intelligence [50]. All tests are widely used in clinical neuropsychological practice and the psychometric properties are well described. Furthermore, the selection

of tests was based on previous neuropsychological studies with cancer patients, to make it possible to compare the results (e.g., [11, 51]). A recent review summarized the most frequently used neuropsychological tests in the assessment of post-chemotherapy cognitive changes in BC patients. Our selection shows overlap with the tests described in this review [51]. The assessments were conducted either at home or in the hospital. Tests were administered in a standardised identical order. The neuropsychological tests were scored independently by two persons. Possible discrepancies between both scores were solved by reaching consensus. The classification of the neuropsychological measures in each domain was based on clinical experience, the descriptives of Lezak, Howieson, Bigner and Tranel [52] and earlier research.

Attention/processing speed: The Stroop test [53, 54] has two conditions for attention: color word reading (card A) and color ink naming (card B). The Trailmaking test condition A [55] is a condition in which a line need to be drawn to connect consecutively numbers. The D2 test [56] is a cancellation task that consists of rows of letters randomly interspersed with a designated target letter. The instruction is to cross out all target letters. The Digit span subtest of the Wechsler Adult Intelligence Scale [57] involves forward and backward repetitions of series of digits. The Digit symbol test of the Wechsler Adult Intelligence Scale [57] is a symbol substitution task. The Fepsy visual reaction test [58] presents stimuli (a white square on the screen at random time intervals measures basic perceptual-motor performance. The Fepsy visual searching test [58] consists of finding one grid pattern out of 24 that matches the one in the center of the screen.

Verbal memory: The Rey auditory verbal learning test [59, 60] is a word list-learning task consisting of five verbal presentations with recall of a 15-word list.

Visual memory: The Visual reproduction subtest of the Wechsler Memory Scale, revised [61] involves the reproduction from memory of geometric designs. The total score is reported. In the Complex figure test [62, 63] patients have to copy a complex figure.

Visuospatial functioning: The copy score of the Complex figure test [62, 63] is used.

Verbal fluency: In the Word fluency subtest [64] patients have to generate words from a specific semantic category (animals and professions) within a limited time.

Executive functioning: In the zoo map test of the Behavioral Assessment of Dysexecutive Syndrome patients [65] have to figure out a route through the zoo following certain rules (map 1) and following a given order (map 2). In the Trailmaking test condition B [55] a line need to be drawn to connect numbers and letters by alternating between the two sequences (condition B). The Fepsy binary choice test [58] gives information about the decision-making process. The patient has to react differentially to stimuli on the screen. The Stroop test [53, 54] card C covers color ink naming of a word denoting a different color.

Motor functioning: The Fepsy finger-tapping task [58] is a measure of motor speed. The speed of finger tapping is measured for both hands separately.

Questionnaires

QoL was measured with the World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100), Dutch version [66]. The WHOQOL-100 is a cross-culturally

developed generic multidimensional QoL questionnaire. It consists of 100 items assessing 24 facets of QoL and a general facet. These facets can be converted into four domains: Physical, Psychological, Social Relations, and Environment. The response scale is a 5-point scale. The time frame of reference is the previous two weeks. The instrument is reliable and valid [67] and the sensitivity of the instrument is also high [68]. Furthermore it is a reliable and valid instrument to measure QoL in women suspected of having BC [69].

The cognitive functioning facet (four items) of the WHOQOL-100, Dutch version [66], was used to assess the satisfaction with SCF, for example with the following question: 'how satisfied are you with your ability to learn new information?' The rating scales range from 1 to 5. A high score on the cognitive functioning facet indicates satisfaction with SCF.

The Cognitive Failures Questionnaire (CFQ) [70], Dutch version [71], was used to assess self-reported frequency of complaints about SCF. This self-report inventory consists of 25 items. The rating scales range from 0 to 4. A high score indicates more often experienced cognitive failure. Earlier research found several two, three and four factor solutions for the CFQ, but none of these factor structures has been validated in a sample of patients with breast problems (e.g., [72-74]).

The Center for Epidemiological Studies-Depression Scale (CES-D) [75], Dutch version [76], was used to measure depressive symptoms. It is a well-established self-report scale designed to measure the presence and degree of depressive symptoms in broad-based survey research populations. It consists of 20 items, with rating scales range from 0 to 3. A higher score indicates more depressive symptoms. The CES-D is a valid and reliable measure of depressive symptoms in BC patients [77].

The Fatigue Assessment Scale (FAS) [78] was used to measure fatigue. It is a 10-item questionnaire that taps fatigue and exhaustion. The response scale is a 5-point scale (1 to 5). A higher score indicates more symptoms of fatigue. The psychometric properties have been studied in different patient populations, including BC patients, and the validity and reliability are reported to be good [79].

The State-Trait Anxiety Inventory (STAI) state scale [80], Dutch version [81], was used to measure anxiety. The state scale asks persons how they feel at a particular moment in time, while the trait scale asks people to describe how they generally feel. In this study the validated shortened 6-item questionnaire for the STAI-state [82, 83] and the validated 10-item version of the STAI-trait [84] were used. The rating scales range from 1 to 4, a higher score indicates more symptoms of anxiety.

The Perceived Stress Scale-10 (PSS-10) [85] was used as a global measure of perceived stress during the last month. It is the shortened version of the PSS-14 and consists of 10 items, rated on a four-point Likert-scale from 0 to 4. A higher score indicates more perceived stress. The validity and reliability of the PSS are good [85].

Outline of the thesis

This thesis is divided into three sections. The first two parts focus on SCF and OCF, respectively. The third part focuses on the impact of cognitive functioning on QoL.

Subjective cognitive functioning

Chapter 2 gives an overview of the studies that have investigated SCF. The prevalence of problems with SCF, the differences between (treatment) groups in problems with SCF, the relationship between problems with SCF and psychological factors, and the relationship between SCF and OCF are examined. Furthermore, this review gives an overview of the used questionnaires to measure SCF. The CFQ is often used in studies concerning SCF in patients with BC. However, the factor structure of the CFQ is still unclear and the psychometric properties were not analyzed for patients with a breast disease before. This is assessed in **Chapter 3**. **Chapter 4** reports SCF across time in BC patients in comparison with BBD patients. Because of heterogeneity in earlier research, both satisfaction *and* frequency of complaints about SCF are evaluated. Furthermore, predictors of SCF are examined.

Objective cognitive functioning

The timing of the baseline measurement in studies concerning OCF often is not standardized. Most longitudinal studies examining the effect of adjuvant chemotherapy on OCF perform the first measurement *before* chemotherapy, but *after* surgical treatment under general anesthesia. It should be recognized that general anesthesia can affect cognitive functioning, also known as post-operative cognitive dysfunction. In **Chapter 5,** the influence of post-operative cognitive dysfunctioning on OCF in BC patients is assessed. Therefore, a group of BC patients receiving neo-adjuvant chemotherapy, i.e., *before* surgery, was included in this study. In addition, the results concerning OCF *before* and three months *after* ending adjuvant chemotherapy in BC patients in comparison with patients with a BBD are described. Besides analyses on group level, changes at the individual level are examined. Furthermore, the relationship between OCF and SCF is explored in this chapter.

Cognitive functioning is generally studied by means of prevalence rates or changes in mean scores over time. However, such an approach may mask subgroups of patients with different courses of cognitive functioning over time. Therefore, **Chapter 6** focuses on identifying longitudinal development classes for OCF in BC patients treated with chemotherapy. Furthermore, the demographic, psychological, and clinical characteristics of these groups are described.

Impact of cognitive functioning on quality of life

Chapter 7 evaluates the course of QoL across time in BC patients treated with chemotherapy compared to patients with a BBD. In addition, the impact of OCF and SCF on QoL is examined.

Chapter 8 contains a summary and discussion of the main findings. Furthermore, methodological considerations, implications for future research and clinical practice are described. Finally, an overview about OCF and SCF in BC patients in Dutch is included in the **Appendix**. This overview especially focuses on the implications for interventions for problems with OCF and SCF.

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Part 1

Subjective cognitive functioning

Chapter 2

Subjective cognitive dysfunction in breast cancer patients: a systematic review

Pullens MJJ

De Vries J

Roukema JA

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Abstract

Objective: Results from studies examining subjective cognitive dysfunctioning (SCD) in breast cancer (BC) patients are unclear. Therefore, this review examined (i) the prevalence of SCD, (ii) the differences between (treatment) groups in SCD, (iii) the course of SCD, (iv) the relationship of SCD with psychological factors, and (v) the relationship between SCD and objective cognitive dysfunctioning (OCD).

Methods: Through a systematic literature-search, we identified 27 studies concerning SCD in BC patients. The methodological quality of these studies was examined according to predefined criteria. The methodological limitations and heterogeneity across studies were taken into account.

Results: Eight studies were graded of high, 12 of moderate, and seven of low quality. Twenty-one to 90% of the patients reported SCD. The comparison between different (treatment) groups, at different time points of the cancer trajectory, rendered inconclusive evidence regarding the relation of SCD to the cancer itself, chemotherapy, and hormonal therapy. SCD and OCD were unrelated, but SCD was associated with psychological distress, fatigue, and health status.

Conclusions: SCD does exist in BC patients, but it remains unclear if this is more commonly found in BC patients than in the general population. It is inconclusive if SCD is developed post-treatment, or already exists pre-treatment. Since there is a relationship between SCD and anxiety and depression, SCD may be more indicative of emotional distress instead of OCD. Attention toward SCD in future research is warranted in order to draw valid conclusions regarding SCD in BC patients.

Key words: cancer, oncology, subjective cognitive dysfunction, self-report, systematic review

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women in the world and comprises 18% of all female cancers [1]. Due to advancements in adjuvant treatment an increasing number of women live with the long-term effects of BC and its treatment [2]. Therefore, it is important to develop a better understanding of the post-treatment effects of adjuvant systemic therapy in BC patients, which involves chemotherapy and/or hormone therapy.

Although adjuvant systemic chemotherapy significantly improves the clinical outcome of patients with early-stage BC, it is also known to have severe side-effects [3]. Apart from common complaints, such as fatigue, hair loss, and depression [4], cognitive impairment after chemotherapy is a reported concern of BC patients [5]. A large proportion of patients treated with chemotherapy will also receive hormonal therapy. There is a growing body of research concerning the influence of chemotherapy and hormonal therapy on neuropsychological functioning in BC patients and survivors (e.g., [5-38]).

Most studies examined objective cognitive dysfunction (OCD) of patients through neuropsychological testing, but the influence of adjuvant chemotherapy and hormone therapy on *subjective* cognitive dysfunction (SCD) has also been assessed by self-reports of patients. SCD refers to the amount of cognitive problems (memory, learning, language, concentration) that patients experience in their daily life and their satisfaction with their cognitive functioning.

The results of the studies examining SCD in BC patients are unclear with regard to (i) the prevalence of SCD, (ii) differences between (treatment) groups in SCD, (iii) the course of SCD, (iv) the relationship of SCD with psychological factors, and (v) the relationship between SCD and OCD. Therefore, the aim of this review was to examine these issues.

Methods

Search strategy

MEDLINE (1263 hits), and PsychINFO (200 hits) databases were searched to identify studies reporting on SCD in BC patients for the period 1960 to April 2009. The term 'breast cancer' was used in combination with other key terms: cognitive / memory /attention / neuropsychological in combination with problems / complaints / dysfunction / self-assessment / self-report / patients' perspective, subjective complaints / decline, and cognitive failure. The reference lists of all identified publications and reviews were checked to capture other relevant publications, which were not identified by the computerized search. Studies reporting an overlap in patient samples were analysed and only the highest quality study was included [20, 21]. When studies described the same patient sample and were of equal quality, only the most recent publication was included [6, 26]. After applying the selection criteria (see below) to the identified articles and their reference articles, 27 studies remained.

Selection criteria

Studies were included if they met the following criteria: (i) described aspects of SCD in BC patients, (ii) the studied population exclusively concerned BC, (iii) the full report of the article was published in English, German, or Dutch. The described inclusion criteria were applied to the initial 1464 hits. Seventy articles met the criteria based on titles of the articles. After inspection of the abstracts and hard copies, 22 articles met our selection criteria and were included in this review. Through hand search, five articles were found (see Figure 1). The included studies were published between 1991 and 2009.

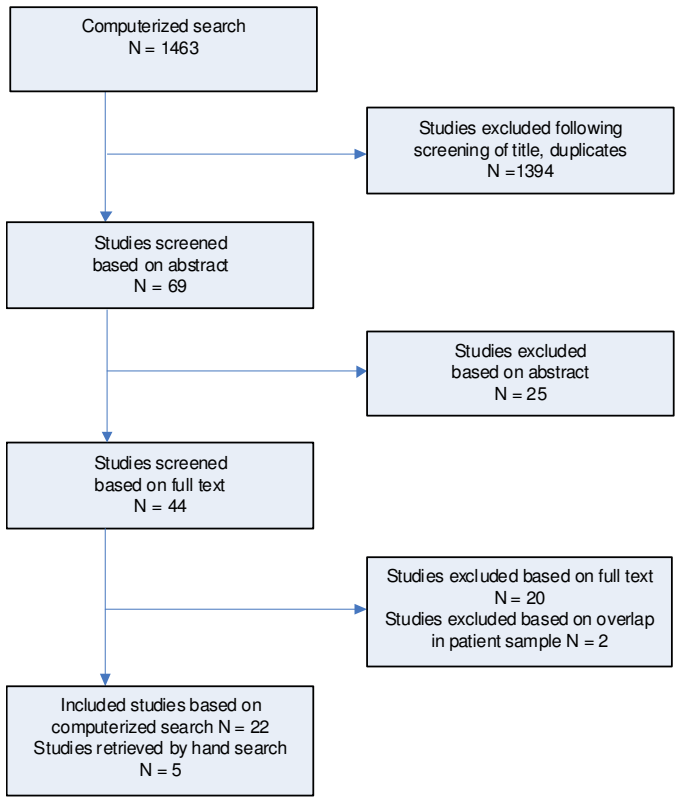

Figure 1: Study selection progress

Quality assessment

The quality of the selected studies was independently assessed using a 17-item predefined checklist (Table 1) by two reviewers (MJJP and JDV). The checklist was based on an established criteria list for systematic reviews [39-42]. For each item in the checklist, studies could be assigned one point. A score of zero points indicated an insufficient or no description of the item. Disagreement about the quality of studies was solved through discussion in a consensus meeting. Studies scoring 70% or more of the maximum score

(≥ 12 points) were considered to be of 'high quality'. Studies scoring between 50% and 70% were rated as 'moderate quality', and scores lower than 50% (≤ 8 points) were considered as 'low quality' studies [42]. Findings were considered consistent if ≥ 75% of the studies that investigated a particular factor showed the same direction of the association. We defined four levels of evidence (Table 2) [42], that we used to describe the results.

Table 1: Criteria list for assessing the methodological quality of studies on subjective cognitive dysfunctioning among BC patients.

Positive if	
Study population	
A.	Patient signed an informed consent form before study participation.
B.	A description is present of at least two sociodemographic data (e.g., age, race, employment status, educational status etc.).
C.	Medical data is described (e.g., tumor stage at diagnosis, treatment etc.).
D.	Inclusion and/or exclusion criteria are formulated.
E.	Participation and response rates for patient groups have to be more than 75%.
F.	Information is presented about patient/disease characteristics of non-responders.
Study design	
G.	Sample size is at least consisting of 50 patients (arbitrarily chosen).
H.	The data collection is described (e.g., neuropsychological assessments, self-report measurements, interview).
I.	Standardized or valid self-report measurements to assess SCD are used.
J.	Definition of SCD is described.
K.	A baseline measurement before treatment.
L.	There are multiple assessment points in time.
M.	Mean or median and range or standard deviation of time before/since diagnosis or treatment is given.
N.	The collection of data is prospectively gathered.
O.	Drop-out rate < 20%.
P.	The study controlled for at least two of the following factors in the results for SCD: depressive symptoms, fatigue, anxiety, stress, menopausal status, influence of hormonal therapy, educational level or age.
Results	
Q.	The results of subjective SCD are compared between two groups or more (e.g., healthy population, different treatment groups, comparison with time and treatment etc.).
R.	Mean, median standard deviations or percentages are reported for the SCD.

SCD = subjective cognitive dysfunctioning

Table 2: Level of evidence

Level of evidence	Description
Strong	Consistent findings (≥ 75%) in at least two high quality studies or one high quality study and at least three moderate studies.
Moderate	Consistent findings (≥ 75%) in one high quality study and at least one low quality study or at least three moderate studies.
Weak	Findings of two moderate studies or consistent findings (≥ 75%) in at least three or more low quality studies.
Inconclusive	Inconsistent findings irrespective of study quality, or less than three low quality studies available.

Results

Study characteristics

The main findings are summarized in Table 3. Considerable variation among the studies with regard to different study characteristics existed. The sample size was often small and ranged from 21 [22] to 1933 [43] patients (mean ± standard deviation = 201.4 ± 452.2). Nineteen studies used a cross-sectional design (four of these studies were longitudinal, but only reported cross-sectional results concerning SCD), seven used a longitudinal design, and one study used a randomised control trial. The timing of assessment in all the studies ranged between 18 days before surgery, to 15.8 years after diagnosis. Most assessments took place within two years after completion of treatment. From the seven studies which reported longitudinal outcomes concerning SCD, five studies included a baseline assessment of SCD before start of treatment (surgery or chemotherapy). Stages of BC, chemotherapeutic agents, doses, duration, and intensity of treatment were heterogeneous *in* and *across* the included studies. Heterogeneity also existed in the inclusion of controls and/or comparison groups. Nine studies did not include a comparison group at all. Different comparison groups were used, e.g., healthy controls, patients with another BC stage, or BC treatment other than chemotherapy.

Only seven out of 27 studies included, described the definition of SCD [9, 11, 38, 44-47]. Some reported a theoretical definition, whereas others reported cut-off points or percentiles that patients need to rate at least in order to consider them as having SCD. A total of 10 different self-report SCD questionnaires were used (Table 4 provides additional information on the SCD questionnaires utilized). Specific measures, as well as subscales from questionnaires that measure another construct, like health status (HS), were used. Nine authors used 'self-made' and non-validated questionnaires and/or semi-structured interviews to examine SCD [9, 11, 13, 22, 23, 25, 44, 48, 49]. A number of other self-report measurements were used to assess psychological factors, such as anxiety, depression, psychological distress, stress, fatigue and HS.

Table 3: Study characteristics

Article	Design	Patient groups	Comparison group	Measurement intervals	Self-report measurement	Subjective results
High quality						
[9]	cross-sectional	N = 39 CT (51% HT)	N = 34 BC without CT	about 2 years post-CT	interview about SCD (memory, attention, thinking, and language) 5-point Likert-scale, EORTC QLQ-C30, HSCL-25	– Significantly more concentration problems: 31%. – Significantly more memory problems: 21%. – No significant group differences in thinking and language. – CT-patients scored significantly higher on SCD in comparison with BC patients without CT. – No relationship between OCD and SCD. – SCD appeared to be related to anxiety and depression.
[20]	cross-sectional	N = 60 CT/RT	N = 83 RT	6 months post-treatment	MASQ	– No significant differences in SCD between RT-patients and RT/CT-patients. – The sample as a whole perceived cognitive problems as happening 'frequently'.
[24]	longitudinal	N = 30 CT	–	baseline, 1 week after completion of 4 CT cycles	AFI, CES-D, STAI, LFS	– Significant decrease over time in SCD (attention). – No significant correlations between SCD and OCD. – Significant correlation between SCD and depression.

Table 3: Study characteristics (continued)

Article	Design	Patient groups	Comparison group	Measurement intervals	Self-report measurement	Subjective results
High quality						
[26]	longitudinal	N = 177 (N = 85 CT; N = 43 HT and/or RT)	N = 49 healthy controls	baseline, post-treatment , 12 months post-treatment	CFQ, GHQ12, FACT-B/F (patients only)/ ES (all groups)	– Psychological distress, QoL and SCD did not influence OCD, but were significantly associated with each other. – No differences in SCD between patients and healthy controls. – CT-patients reported significant more SCD post-treatment compared to the baseline. – HT and/or RT patients showed no significant differences between the measurement intervals on SCD. – No significant correlation between OCD and SCD. – 83% Reported memory problems and 80% concentration problems post-CT It decreased post-CT, but memory problems were increased at 12 months post-CT compared with post-CT. 45% Reported memory problems and 38% concentration problems post-HT and/or RT.
[28]	longitudinal	N = 109 neo-adjuvant-CT	–	baseline, toward the end of neo-adjuvant-CT	FEDA, EORTC QLQ-C30, HADS	– No significant relationship between OCD and SCD, anxiety, depression, and menopausal state. – All correlations of anxiety and depression with SCD were significant and of moderate size. – At baseline, a subgroup showed cognitive compromise that was unrelated to anxiety or depression. – Significant increase in SCD toward end of CT compared with baseline assessment.

Table 3: Study characteristics (continued)

Article	Design	Patient groups	Comparison group	Measurement intervals	Self-report measurement	Subjective results
High quality						
[29]	longitudinal	N = 45 CT (76% HT)	–	baseline, 6 months post-CT	SSRQ	– Patients who perceived a poorer memory than average at baseline reported further memory deterioration post-CT (63%). – 27% of the patients with a (better than) average perceived memory perceived memory deterioration after CT. – The ability to learn new information was the most affected domain (49%).
[45]	cross-sectional	N = 80 (N = 30 CT and Tamoxifen; N = 50 CT and Exemestane)	N = 48 healthy controls	2 years post-treatment	interview with Likert-scale, CFQ, EORTC-QLQ-C30, HSCL-25, MFI-20, FACT-B/ES	– Patients reported significantly more memory complaints (25%) than controls (6%). – No differences in proportion of patients reporting memory complaints between patients receiving Tamoxifen (28%) and Exemestane (24%). – No group differences regarding complaints about concentration, thinking and language between patients and controls. – SCD shows significant correlations with anxiety, depression, fatigue and menopausal symptoms, but not with OCD and time since treatment.

Table 3: Study characteristics (continued)

Article	Design	Patient groups	Comparison group	Measurement intervals	Self-report measurement	Subjective results
Moderate quality						
[11]	longitudinal	N = 76 (sometimes with HT) (N = 22 CTC; N = 23 FEC; N = 31 CMF)	N = 27 no CT	about 2 and 4 years post-treatment	interview about SCD (memory, attention, thinking, and language) 5-point Likert-scale, EORTC QLQ-C30, HSCL-25	– No significant differences in SCD between CTC/FEC group and controls 4 years post-treatment. – No group differences 4 years post-treatment on fatigue, depression, and EORTC QLQ-C30 between patients and controls. – CMF group differed significantly in memory, concentration, depression, anxiety compared with controls four years after CT. – Low correlations between OCD and SCD (0.19-0.22).
[13]	randomized-control trail	N = 70 CT (sometimes with HT/RT; N = 34 high-dose CT; N = 36 standard dose CT)	N = 34 no CT	at least 6 months after CT	interview with Likert-scale, EORTC QLQ-30, HSCL	– No significant differences in SCD between high dose- and standard dose CT. – CT-patients reported significantly more concentration, memory and thinking problems compared with controls. – Patients with high dose CT reported more fatigue and depressive symptoms compared with the control group. – No correlation between OCD and SCD. – Significant relationship between SCD and anxiety and depression.

Table 3: Study characteristics (continued)

Article	Design	Patient groups	Comparison group	Measurement intervals	Self-report measurement	Subjective results
Moderate quality						
[19]	cross-sectional	N = 53 (N = 17 local therapy; N = 36 CT (sometimes with HT)	N = 19 healthy controls	between 2 to 5 years post diagnosis	CFQ, BDI-II, STAI, 4 items of the MOS-SF-36	– No relationship between OCD and SCD, except for the relationship between visuospatial performance and SCD. – SCD was associated with depression, anxiety and fatigue.
[27]	longitudinal *	N = 46 (N = 19 CT; N = 15 CT/HT)	N = 12 DCIS, no CT or HT	baseline, within 1 week after CT; one year post-CT	PAOF, BDI-II, POMS	– No correlations between OCD and SCD. – Significant relationship between depression and SCD. – No between groups differences in SCD 1 week and 1 year post-CT – CT/HT-patients reported significantly more memory complaints one year post-treatment, compared with CT-patients.
[30]	cross-sectional	N = 47 CT/RT and sometimes HT (N = 23 standard-dose CT; N = 24 high-dose CT)	N = 29 RT	5 years post-treatment	FEDA, MFI-20, EORTC QLQ-C30	– OCD is not associated with SCD, fatigue and health related QoL. – SCD: 46%. – No between group differences in SCD. – Distractibility and retardation in mental processes: 37% – Decrease in drive: 29%.

Table 3: Study characteristics (continued)

Article	Design	Patient groups	Comparison group	Measurement intervals	Self-report measurement	Subjective results
Moderate quality						
[32]	longitudinal *	N = 90 CT (sometimes with RT or HT)	–	9 months post-treatment	EORTC QLQ-C30, MFI-20, HADS, FEDA	– Significantly low correlation between HADS and self-appraisal scales of cognitive function. – SCD: 36% of the patients. – 11% is impaired on both OCD and SCD, 24% only on SCD and 10% only on OCD.
[38]	cross-sectional	N=52	N = 500 healthy controls	between 1.2 to 15.8 years post-treatment	CES-D, SSRQ	– Memory impairment: 14%. – The patients with SCD did not perform differently from non-SCD on OCD and depression.
[43]	cross-sectional	N = 1933 (N = 634 breast-conserving surgery; N = 1299 mastectomy)	N = 52 matched healthy controls	50 months after surgery	EORTC QLQ-C30 in combination with the EORTC QLQ-BR-23, MQoL, BFI, BDI	Clinically significant differences in SCD between disease-free survivors and the general female population.
[48]	cross-sectional	N = 150 disease free BC patients CT or RT or CT/RT (N = 57 severely fatigued; N = 93 non-severely fatigued)	N = 78 healthy controls	between 6 to 60 months post-treatment	daily self-observation list for concentration and memory, CIS, SIP-8	– Severely fatigued patients reported more SCD (except memory) compared with non-severely fatigued patients and controls. – SCD did not differ between the different BC-treatments.

Table 3: Study characteristics (continued)

Article	Design	Patient groups	Comparison group	Measurement intervals	Self-report measurement	Subjective results
Moderate quality						
[49]	longitudinal	N = 93 CT (sometimes with HT and/or RT)	N = 49 no CT	1 month and 1 year post-treatment	interview data	– Memory problems: 71% 1 month post-treatment, 60% 12 months post-treatment. – Concentration problems: 64% 1 month post-treatment, 42 % 12 months post-treatment. – No relationship between OCD and SCD, but an association with psychological distress and quality of life was found. – CT-patients reported more memory and concentration problems 1 month post-treatment compared with patients without CT. – CT-patients did not differ from patients without CT 1 year post-treatment on memory and concentration problems.
Low quality						
[22]	cross-sectional	N = 21 CT	–	2-6 weeks after their previous CT	FACT-G/F/ES, semi-standardized interview	– All patients experienced fatigue. – Most patients noted adverse changes in SCD (concentration), with substantial effects on every-day function.
[23]	cross-sectional	N = 201 CT (sometimes combined with HT)	N = 172 RT (sometimes combined with HT)	6 to 11 years post-treatment	a self-constructed QoL questionnaire	– Memory problems: 37% of RT-patients and 36% of CT-patients. – Concentration problems: 30% of RT/CT-patients.

Table 3: Study characteristics (continued)

Article	Design	Patient groups	Comparison group	Measurement intervals	Self-report measurement	Subjective results
Low quality						
[25]	longitudinal *	N = 36 CEF (53% combined with HT)	N = 14 cardiac patients; healthy controls	before CT, 4 to 6 weeks post-treatment	PSS, BDI, SSQT, SLS, POMS, PSI, interview about SCD (concentration, attention, memory) 5-point Likert-scale	– Higher depression scores at follow-up were associated with greater SCD (attention). – No relationship between SCD and OCD (except for attention). – BC patients reported significant more SCD (memory and concentration) compared to healthy controls.
[33]	cross-sectional	N = 94 HT (67% combined with RT)	N = 35 healthy controls	–	BDI, GHQ-12, CFQ	– High depression scores were significantly associated with SCD. – SCD was not related to OCD.
[45]	cross-sectional	N = 31 HT (58% combined with CT)	–	receiving HT at least for 3 months	PAOF	– Poorer SCD is marginally associated with better visual learning, verbal memory, attention and mental flexibility.
[51]	longitudinal *	N = 109 (N = 39 CT/RT; N = 45 RT/HT; N = 19 RT)	–	at initiation, at the end, 6 weeks after completion RT	EORTC QLQ-C30/BR23	– Significantly more SCD in RT/CT-patients, compared with RT- and RT/HT-patients. – No significant difference in SCD between patients treated with RT/HT-patients and RT-patients.

Table 3: Study characteristics (continued)

Article	Design	Patient groups	Comparison group	Measurement intervals	Self-report measurement	Subjective results
Pre-treatment						
[46]	cross-sectional	N = 74	–	11 to 17 days before surgery	SDS, AFI, POMS	– 27% Perceived effective cognitive functioning. – Relation between more SCD and greater mood disturbance.
[47]	cross-sectional	N = 184 stage 0-II	–	18 days before surgery	AFI, SDS, POMS-SF	– No significant correlation between OCD and self-reports of effectiveness in cognitive functioning. – Distress was not associated with OCD. – Significant predictors of perceptions of effectiveness in cognitive functioning: symptom and mood distress. – No significant relation between education-level and attention. – Pre-menopausal patients significant lower effectiveness in cognitive functioning. – Perceived cognitive functioning: 25% effective, 50% moderate, and 25% lower effectiveness.
[50]	cross-sectional	N = 132 (N = 110 stages 1-3; N = 22 stage 0)	N = 45 healthy controls	after surgery but prior to beginning additional therapy	CED-D, STAI, FSI, MASQ	– No group differences on the MASQ total score or any subscale. – Patients scored significantly higher on the depression, anxiety and fatigue, compared with controls. – No significant correlation between OCD and SCD.

Table 3: Study characteristics (continued)

AFI = Attentional Function Index; BDI = Beck Depression Inventory; BFI = Brief Fatigue Inventory; CEF = Cyclophosphamide-Epirubicine-Fluorouracil; CES-D = Center for Epidemiological Study: Depression; CFQ = Cognitive Failure Questionnaire; CIS = Checklist Individual Strength; CMF = Cyclophosphamide-Methotrexate-Fluorouracil; CT = Chemotherapy; CTC = Cyclophosphamide-Thiotepa-Carboplatin; EORTC QLQ-C30/BR23 = European Organization for Research and Treatment of Cancer quality of life core questionnaire/Breast Cancer specific; FACT-G/F/ES = Functional Assessment of Cancer Therapy-General/Fatigue/Endocrine Symptoms; FEC = Fluorouracil-Epirubicin-Cyclophosphamide; FEDA = Fragebogen erlebter Defizite der Aufmerksamkeit; FSI = Fatigue Symptom Inventory; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; (questionnaire of experienced attention deficits); HSCL-25 = Hopkins Symptom Checklist-25; HT = Hormonal therapy; LFS = Lee Fatigue Scale; MASQ = Multiple Ability Self-report Questionnaire; MFI-20= Multidimensional Fatigue Inventory; MOS-SF-36 = Medical Outcomes Study Short Form-36; MQoL= Multidimensional Health Related Quality of Life; PAOF = Patient's Assessment of Own Functioning; POMS(SF) = Profile OF Mood States (Short Form); PSI = Pittenburgh Sleep Inventory; PSS = Perceived Stress Scale; QoL = Quality of Life; RT = Radiation therapy; SDS = Symptom Distress Scale;SIP-8 = Sickness Impact Profile; SLS = Satisfaction with Life Scale; SSQT = Social Support Questionnaire of Transactions; SSRQ = Squire Memory Self Rating Questionnaire; STAI = State Trait Anxiety Inventory.

* Cross-sectional concerning the results for SCD

Table 4: Used SCD questionnaires

Questionnaire	**Standardized/ valid questionnaire**	**Study**	**Remark**
Fragebogen erlebter Defizite der Aufmerksamkeit (questionnaire of experienced attention deficits) (FEDA) [58]	yes	[28, 30, 32]	Psychometric properties were tested in schizophrenic and depressive patients.
Multiple Ability Self-report Questionnaire (MASQ) [59]	yes	[20, 50]	
Patient's Assessment of Own Functioning (PAOF) [60]	yes [60]	[27, 45]	
Cognitive Failure Questionnaire (CFQ) [61]	yes [62, 63]	[19, 26, 31, 33, 45]	
Attentional Function Index (AFI) [64]	no	[24, 46, 47]	
Squire Memory Self Rating Questionnaire (SSRQ) [65]	no	[29, 38]	
European Organization for Research and Treatment of Cancer quality of life core questionnaire (EORTC QLQ-C30) [66]	yes	[9, 11, 13, 28, 30-32, 43, 45, 51]	Subscale cognitive functioning.
European Organization for Research and Treatment of Cancer quality of life Breast Cancer Specific (EORTC QLQ-BR23) [67]	yes	[43, 51]	Subscale cognitive functioning.
Multidimensional Fatigue Inventory (MFI-20) [68]	yes	[30, 32]	Four items focusing on attention. Psychometric properties were tested in cancer patients receiving radiotherapy.
Semi-standardized interview/ self-constructed questionnaire	no	[9, 11, 13, 22, 23, 25, 45, 48, 49]	Likert-scales for cognitive domains.

Methodological quality

Eight studies were graded as high [9, 20, 24, 26-29, 44], 12 as moderate [11, 13, 19, 30-32, 38, 43, 47-50], and seven as low methodological quality [22, 23, 25, 33, 45, 46, 51]. The quality scores ranged from six (low) to 14 (high) (mean ± standard deviation = 10 ± 2.2). Methodological shortcomings mainly concerned the following items: 25 studies did not control for at least two confounding factors in the results for SCD, 23 studies did not provide patient/disease characteristics of non-responders, 21 studies did not have a participation rate exceeding 75%, 20 studies did not describe a definition of SCD, 20 studies did not have a baseline measurement before treatment, and 16 studies did not provide information of time since/before diagnosis or treatment.

Prevalence of subjective cognitive dysfunctioning

Eleven studies described percentages of prevalence of SCD ranging from 21% to 90%. The proportion of patients with SCD varied widely, reflecting differences in definitions, instruments utilized and cut-off points. SCD consisted of problems with memory (range between 14% and 95%) [9, 22, 23, 26, 29, 38, 44, 49], concentration (31% to 90%) [9, 22, 23, 26, 49], language (78%) [22], and self-reported retardation in mental processes or lower effectiveness (25% to 47%) [30, 47].

Subjective cognitive dysfunctioning in breast cancer patients versus healthy controls

Evidence regarding differences in SCD between BC patients and healthy controls remains inconclusive. Five studies (one high, three moderate and one low methodological quality), found significantly more SCD in BC patients treated with chemotherapy, sometimes combined with hormone therapy and/or radiotherapy, compared with healthy controls at different time periods after treatment (six weeks, three and six months, and two and four years post-treatment) [13, 25, 31, 43, 44]. Two high quality studies did not find significant group differences in BC patients treated with chemotherapy, radiation therapy, and/or hormone therapy compared with healthy controls at one and two years after treatment [26, 44].

Subjective cognitive dysfunctioning in different treatment types

Evidence regarding differences between treatment types in SCD remains inconclusive. Four studies found evidence for group differences, but 10 studies did not find significant differences between treatment groups in SCD. Multiple differences were found in SCD between different treatment types. One study (moderate quality) found significant differences in SCD between patients treated with chemotherapy (sometimes with hormone therapy and/or radiotherapy) and patients treated without chemotherapy one year post-treatment [49]. Another study (moderate quality) found that women who received chemotherapy and hormonal therapy reported significantly more memory complaints one year after completing chemotherapy compared with women who received chemotherapy alone [27]. Furthermore, one moderate quality study found significantly more memory and concentration problems in BC patients treated with cyclophosphamide/methotrexate/5-fluorouracil (CMF) compared with lymph node-

negative BC patients (not treated with chemotherapy), four years after treatment [11]. One low quality study found more SCD in patients treated with radiotherapy in combination with hormone therapy compared to patients treated with only radiotherapy six weeks after ending radiotherapy [51].

Ten studies did not find significant differences between treatment groups in SCD [9, 11, 13, 20, 27, 30, 44, 48, 49, 51]. Patients treated with high dose chemotherapy were compared with standard dose treated patients [13]. Other studies compared patients treated with chemotherapy and/or radiotherapy and/or hormonal therapy with patients treated with radiotherapy only [20, 27, 30, 48] or radiotherapy which was sometimes combined with hormone therapy [9]. No significant differences were found in a high and moderate quality study that compared different chemotherapies and hormonal therapies [11, 44].

The course of subjective cognitive dysfunctioning

To examine if SCD exists due to systemic treatment or if it already exists pre-treatment after the patient is informed about the BC diagnosis, we looked at the pre-treatment results of SCD. Eight studies assessed the patients' SCD prior to the start of systemic therapy. Most of these studies were longitudinal and of high or moderate quality [24, 26, 28, 29, 31]. Three studies (low to moderate quality) focussed only on the pre-treatment assessment [46, 47, 50]. There was no major dissimilarity between the pre- and post-treatment occurrence of SCD. Strong evidence is found for the increase of the severity of SCD directly after systemic treatment compared with baseline measurements [24, 26, 28, 29, 31]. Fluctuating and inconclusive results were found for changes in severity and occurrence of SCD over time after treatment [24, 26, 31, 49].

Relationship between subjective and objective cognitive dysfunctioning

Strong evidence was found for the lack of a relationship between SCD and OCD. Fifteen studies evaluated the correlation between SCD and OCD, eleven of these studies did not find a significant correlation between the self-reports of the women and the outcome scores of the neuropsychological assessment [9, 13, 19, 24, 26-28, 30, 44, 49, 50]. Some studies (low to moderate quality) found a significant relationship between SCD and different domains of OCD: working memory [30], visuospatial ability [19], attention [25, 45], visual learning, verbal memory and mental flexibility [45]. One moderate quality study found low correlations between SCD and OCD (.19 - .22) [11].

Relationship between subjective cognitive dysfunctioning and psychological factors

The lack of correlation between OCD and SCD suggests that the SCD may be more indicative of emotional distress than cognitive dysfunction. Studies which explored the effect of psychological factors on cognitive functioning, found moderate evidence for a relationship between SCD and anxiety between the end of chemotherapy and nine months later [13, 28, 32], and strong evidence was found two years after completion of systemic therapy [9, 44]. In addition, moderate evidence for the relationship between SCD and depression was found for six months [13, 24], weak evidence was found between nine

and 12 months [27, 32], and strong evidence was found two years after completion of systemic therapy [9, 44]. Studies that focused on general psychological distress found moderate evidence for the relationship with SCD between 12 and 18 months post-treatment [26, 49]. Moderate evidence was found for the relationship between fatigue and SCD between two and five years after completion of systemic therapy [19, 44]. Furthermore, one moderate quality study found significantly more SCD in severely fatigued patients compared with non-severely fatigued BC patients and controls [48]. For the relationship between SCD and HS, moderate evidence was found between 12 and 18 months post-treatment [26, 49].

Discussion

This systematic review, examined the prevalence of SCD, the differences between (treatment) groups in SCD, the relationship of SCD with psychological factors, and the relationship between SCD and OCD. Strong evidence was found for the lack of a relationship between OCD and SCD. Methodological limitations and heterogeneity of the existing studies made it difficult to draw further definitive conclusions. The reported prevalence of SCD varied considerably, which is most likely the result of the variety in definitions, questionnaires, and cut-off scores. SCD does exist in the BC population, but inconclusive evidence was found for the comparisons with other populations, so it is unclear if SCD is more commonly found among BC patients than in the general population. Due to the heterogeneity in systemic treatments, no specific results could be reported concerning the effects of individual treatment modalities on SCD (e.g., the exact effect of chemotherapy or hormonal therapy alone).

This review did not find evidence for differences in the prevalence of SCD between post- and pre-treatment assessments, which implies that there is no effect of systemic treatment on the occurrence of SCD. Evidence was found for short time increased severity of SCD directly after systemic treatment, compared to the baseline assessment, but inconclusive evidence was found for the course of SCD after treatment. The evidence for the differences in the occurrence of SCD between pre- and post-treatment assessments and the course of SCD after treatment was probably lacking because most longitudinal studies focused on OCD and therefore did not provide the results of SCD over time. At this moment it is still unknown whether SCD already exists before the BC diagnosis, so it remains unclear whether the pre-treatment SCD is due to stress, related to the diagnosis, or if it is just a symptom that exists in the general population and is not specifically related to BC.

While there is an increasing number of studies focusing on OCD in BC patients, more attention needs to be paid to SCD as well. As stressed by Castellon et al., both OCD and SCD should be examined [19]. This review supports this statement because we found strong evidence for a lack of a relationship between OCD and SCD, but both are relevant topics in order to investigate cognitive functioning in BC patients. There are a number of possible explanations for this lacking relationship. First, the neuropsychological tests may

be insufficiently sensitive to detect mild OCD in patients treated for cancer, because these tests are routinely used with groups of patients with degenerative decline or other brain injuries [52, 53]. A second explanation could be that, except for the longitudinal designs of some included studies, objective tests evaluate performance at a point in time, whereas self-report encompasses assessment of performance over a broader period (e.g., patients need to rate how often they had suffered from memory problems the last month) [54]. Third, increased knowledge about the relationship between chemotherapy and cognitive dysfunction could influence the expression of SCD. Schagen et al. examined the influence of knowledge about the 'chemo-brain schema', which is described as the cognitive representation of past experience, knowledge, and expectancies (explicitly informed or due to pre-existing knowledge) [53]. They found an increase in SCD in patients with pre-existing knowledge about chemotherapy-associated cognitive problems compared with patients without this knowledge [53]. Fourth, subjective measures and neuropsychological tests do not measure the same construct. Objective performance on tests may not accurately reflect the SCD that many women experience after treatment of BC. Alternatively, reported SCD may indicate emotional distress instead of real cognitive problems [52], and is a way in which a patient copes with stressful events [53].

This review found evidence for the association of SCD with anxiety, depression, psychological distress, fatigue, and lower HS. It is unknown if the existing cognitive problems lead to psychological distress or if psychological distress leads to the persistence of cognitive problems. Cognitive problems may indicate psychological distress: diminished ability to think and concentrate is one of the possible symptoms of a depressive episode, and concentration problems could be a symptom of an anxiety disorder [55]. Literature has shown a negative influence of chemotherapy and hormonal therapy on fatigue and OCD [14, 56] and fatigue is found as the most important predictor of SCD [57]. Thus, this overlap between the symptoms of SCD and anxiety, depression and fatigue is a valuable explanation for the association of SCD with these constructs. It is likely that SCD is more a reflection of psychological symptoms instead of OCD.

There are several shortcomings in the available studies. The cross-sectional nature of many included studies limits conclusions of causality and the development of SCD over time. The lack of baseline measurements made it difficult to make inferences regarding a real increase of SCD after systemic treatment. The small patient populations, lack of control groups, and lack of controlling for confounding variables were other shortcomings. Prospective longitudinal follow-up research with a baseline measurement, more patients, and a control group is needed in order to draw valid conclusions regarding SCD in BC patients. In order to accomplish this, studies should use a validated instrument and cut-off points to measure SCD. Anxiety, depressive symptoms, fatigue, and quality of life should be topics in future research elucidating the persistence of these post-treatment SCD in BC patients.

Self-report measures are important to understand the BC patients' perspective of the experienced problems. Despite the inconsistent results concerning the persistence and prevalence of SCD in BC patients and the relation with psychological distress, it should be assessed and intervened upon in clinical practice. This is necessary because patients do

express their concerns regarding SCD and this review found evidence for the presence of SCD in BC patients.

In conclusion, SCD does exist in BC patients, but it remains unclear if this is due to systemic treatment or to the stress related to the diagnosis of BC. Since there is no relationship between SCD and OCD and there is evidence for relationships between SCD and anxiety, depression, and HS, SCD may be more indicative of emotional distress. Attention toward SCD in future high quality research is needed in order to draw definitive conclusions.

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Chapter 3

Subjective cognitive functioning in patients with a breast disease: the cognitive failures questionnaire

Pullens MJJ

De Vries J

Bogaarts MP

Roukema JA

Submitted for publication

Abstract

Purpose: To gather useful information about subjective cognitive functioning among patients with a breast disease, the cognitive failures questionnaire (CFQ) have been frequently used, although its factor structure is still unclear. This study examines the factorial representation and psychometric properties of the CFQ in this population.

Methods: The CFQ was completed by 180 women with a breast disease. Furthermore, all participants completed measures of state anxiety, depression, fatigue, and the satisfaction with cognitive functioning. For each of the existing factor structures a confirmatory factor analysis was conducted to examine the fit of the factor structures of the CFQ. Furthermore, an exploratory factor analysis was done.

Results: None of the existing models met the criteria for an acceptable fit in the sample of patients with a breast disease. The three-factor model (Forgetfulness, Absentmindedness, and Social recklessness) derived from the exploratory technique showed good reliability and validity.

Conclusions: The CFQ with the three-factor model is an adequate instrument for measuring the frequency of everyday cognitive lapses in women with a breast disease.

Keywords: Cognitive failures questionnaire, cognitive functioning, factor structure, breast cancer, benign breast disease

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women in the developed countries. In the Netherlands, one in nine women will develop BC during her life [1]. Women who feel an abnormality in their breast or women whose screening mammography is abnormal are referred for further examination. This will result in the diagnosis BC or a benign breast disease (BBD). In addition to surgery, BC patients are often treated with adjuvant therapies, such as chemotherapy. During and after this adjuvant treatment, complaints of cognitive functioning are frequent among BC patients (see Wefel and Schagen for a recent overview [2]). While most studies focus on objective cognitive functioning (OCF) in BC patients, some investigators are also interested in subjective cognitive functioning (SCF) (e.g., [3-5]). SCF refers to the cognitive problems that persons experience in their daily life and their satisfaction with their cognitive functioning. When examining cognitive functioning in patients with a breast disease, it is important to assess both OCF and SCF, as strong evidence is found for the lack of a relationship between OCF and SCF [6]. However, there is some literature that supports the ability that individuals have to subjectively detect changes in cognitive function before they are documented with objective neuropsychological tests [7]. Thus, there might be a relationship between SCF and subsequent cognitive decline in particular populations. Therefore, the assessment of SCF in patients with breast disease can be of great importance as predictor for longitudinal cognitive outcomes of patients.

Earlier research regarding SCF in BC patients did not find differences between BC patients and healthy controls. One of our suggestions is that problems with SCF may be more indicative of emotional distress than problems with OCF [6]. However, another hypothesis is that differences between patients with a breast disease and the healthy population are not found because problems with SCF should be measured with a validated factor structure for patients with a breast disease.

Various measures have been used in assessing SCF in patients with a breast disease (both BC and BBD). There are specific measures and subscales from questionnaires that measure another construct, such as quality of life. Furthermore, investigators use ad hoc, non-validated questionnaires and/or semi-structured interviews to examine SCF (see Pullens, De Vries, and Roukema for an overview [6]). One of the specific measures that is available in many languages, such as Dutch, is the Cognitive Failures Questionnaire (CFQ) [8]. It is a 25-item scale that assesses the self-perceived frequency of cognitive dysfunctions in daily life by reporting the frequency of incidents on a 5-point scale.

To gather useful information about SCF among patients with a breast disease, it is important to use assessment tools that are reliable and validated. Although the CFQ have been used several times to assess SCF in patients with a breast disease [3, 9-11], its factor structure is still unclear. A number of factor analyses have been conducted in different samples to capture the structure of the CFQ. Although Broadbent, Cooper, FitzGerald and Parkes [8] assumed that a general factor adequately described the CFQ, others found more than one factor [12-19]. The findings of these different factor analyses are contrasting.

Furthermore, no information is available about the factor structure for patients with a breast disease. This information could be helpful in the investigation of problems with SCF in patients with a breast disease. Therefore, the first aim of the present study was to find a factorial representation of the CFQ in a population of women with a breast disease (both malignant and benign problems) by examining known factor structures and using an exploratory technique. Furthermore, the psychometric properties of the factor structure for patients with a breast disease were examined.

Methods

Participants and procedure

Women who were diagnosed with BC and received chemotherapy between January 2009 and January 2011 in St. Elisabeth hospital (Tilburg), TweeSteden hospital (Tilburg), Maxima Medical Centre (Eindhoven, Veldhoven), Catharina hospital (Eindhoven), St. Anna hospital (Geldrop), Amphia hospital (Breda), and Jeroen Bosch hospital (Den Bosch) were eligible for this study. In addition, women diagnosed with a BBD were also asked to participate. A cyst, mastopathy or a fibro-adenoma are the most common BBD diagnoses. Treatment of the BBD is not necessary for most women but some women are invited for a follow-up examination several months later. Furthermore, some women want their cyst or fibro-adenoma to be surgically removed.

Women with proven BC recurrence or distant metastases were excluded. Other exclusion criteria were related to the assessment of OCF with neuropsychological tests (these results will be described elsewhere): a history of neuropsychological and/or psychiatric signs or symptoms that lead to deviant neuropsychological test results (e.g., dementia), the use of medication that may lead to deviant neuropsychological results, alcohol and/or drug addiction, and a poor expression in the Dutch language.

When women were invited to participate in the study, the diagnosis was known, but no adjuvant treatments were started yet. All participants provided written informed consent and this study was approved by a central medical ethic committee.

Materials

All patients were asked to report a number of sociodemographic aspects (age, living with partner, having children, educational level, having salaried work/retirement) and completed the following questionnaires after diagnosis is known.

The Cognitive Failures Questionnaire (CFQ) [8], Dutch version [20] was used to assess cognitive failure on everyday tasks (e.g. memory, perception, and motor control). This self-report inventory consists of 25-items assessing the frequency of cognitive slips during the last six months. The rating scale is a 5-point Likert-scale. High scores indicate high levels of cognitive failure.

The cognitive functioning facet of the World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100) [21], Dutch version [22], was used to assess satisfaction with SCF. The WHOQOL-100 consists of 100 items assessing 24 facets of QoL,

four questions each, that combined compile QoL. QoL refers to the evaluation of function, e.g., satisfaction with aspects of life. The cognitive functioning facet measures satisfaction with SCF, for example with the following question: 'how satisfied are you with your ability to learn new information?' The rating scales range from 1 to 5. A high score on the cognitive functioning facet indicates satisfaction with SCF. The instrument is reliable and valid [23] and the sensitivity of the instrument is high as well [24].

The Center for Epidemiological Studies-Depression Scale (CES-D) [25], Dutch version [26], was used to measure the presence and degree of depressive symptoms. It consists of 20 items. The rating scales range from 0 to 3. A higher score indicates more depressive symptoms. An indication of a depression was defined as a score above 16 [27]. The CES-D has been established as a valid and reliable measure of depressive symptoms in BC patients [28].

The Fatigue Assessment Scale (FAS) [29] was used to measure fatigue. It is a 10-item questionnaire that taps fatigue and exhaustion. The response scale is a 5-point scale (1 to 5). A higher score indicates more symptoms of fatigue. High fatigue was defined by a score above 21 [29]. The psychometric properties have been studied for different patient populations including BC patients and are reported to be good [30].

The State-Trait Anxiety Inventory-state (STAI) [31], Dutch version [32] was used to measure anxiety. The state scale asks persons how they feel at a particular moment in time, while the trait scale asks people to describe how they generally feel. In this study the validated shortened 6-item questionnaire for the STAI-state and the 10-item version of the STAI-trait was used. The response scale is a 4-point scale (1 to 4). A higher score indicates more symptoms of anxiety. High state anxiety was defined as a score above 14, high trait anxiety was defined as a score above 22 [33-35].

Statistical analyses

Calculation of frequencies was used to present the demographic and psychological data of the total group. Independent sample t-tests (continuous data) and χ^2-tests (nominal data) were used to examine potential differences between the BC patients and the BBD patients.

Confirmatory factor analyses (CFA) were conducted to test the structures found in earlier research. Goodness of fit was verified by the following fit indices: the Comparative Fit Index (CFI) and the Root Mean Square Error of Approximation (RMSEA). The models have a satisfactory to good fit when CFI > 0.90 and RMSEA < 0.06 [36].

An exploratory factor analysis (EFA) (principal axis factoring), followed by varimax rotation, was conducted to find an adequate and interpretable dimensional representation of the CFQ in our sample of patients with a breast disease. Frequencies were employed for calculating the skewness and kurtosis of the CFQ questions. Items were excluded from this EFA when the converted z-scores of both the skewness as the kurtosis were greater than 1.96. The interpretation of the scores on these items showed that there is almost no variation in the score between the participants on these items. A combination of the scree test and interpretability was used to choose the number of

factors. Items with cross-loadings were excluded when the difference between the factor loadings was smaller than .15.

The internal consistency for each factor was estimated using Cronbach's alpha coefficients. Depending on the number of items in a scale, values should be at least 0.70 [37]. In order to provide information on construct validity, Pearson's correlation coefficients were calculated between the CFQ and the CES-D and STAI-state to examine the divergent validity. To examine the convergent validity, Pearson's correlation coefficients between CFQ and the cognitive functioning facet of the WHOQOL-100 and the FAS were calculated. Fatigue was chosen because an association is found between fatigue and cognitive complaints (e.g., [38]). We did not use a neuropsychological test to examine convergent validity, because the literature is consistent about the lack of a relationship between OCF and SCF [6]. Moderate (r = 0.30 - 0.49) and high (r = > 0.49) correlations are indicative for convergent validity, whereas small correlations (r = 0.10 - 0.29) are indicative for divergent validity [37]. The data were processed by means of the Statistical Package for the Social Sciences (version 17.0 for Windows), except for the CFA (AMOS 17.0).

Results

Patient characteristics

In total, 180 patients with a breast disease completed the questionnaires; 91 BC patients and 89 BBD patients. The baseline psychological factors showed a significantly lower score on fatigue in BC patients. The percentages of fatigued patients also differed significantly between BC and BBD patients. In addition, a higher score on state anxiety in patients with BC was found, however, the percentages of patients scoring high on state anxiety did not significantly differ between BC and BBD patients. Furthermore, significant differences in educational level were found between BC and BBD patients. BC patients and BBD patients did not significantly differ on the original CFQ-25 item version. No additional significant differences were found concerning sociodemographic factors and the remaining psychological factors and classifications in 'high trait anxiety' and 'indication of a depression' (see Table 1).

Confirmatory factor analyses

Ten studies in which the factor structure of the CFQ was identified were found in the literature [8, 12, 14-20]. For each of these factor structures a CFA was conducted to examine the fit of the factor structures of the CFQ. None of the models met the criteria for an acceptable fit. Table 2 gives an overview of the tested factor structures.

Exploratory factor analysis

Five questions were excluded before the EFA because the z-scores of both skewness and kurtosis were higher than 1.96: item 4 (confuse right and left), 5 (bump into people), 18 (throw away something you want to keep), 19 (daydream), and 24 (drop things). The scree plot of the EFA revealed three factors. Based on the factor loadings, items 13 (feel to see a

product in supermarket), 15 (trouble making up your mind), 12 (forget which way to turn on a road), and 21 (start doing one thing and get distracted into doing something else) were excluded because the difference between the cross-loadings of these items with other factors was smaller than .150. The three-component solution explained 37.2% of the variance, with factor one (Forgetfulness) contributing 16.0%, factor two (Absent-mindedness) contributing 11.3%, and factor three (Social recklessness) contributing 9.9%. The EFA results are presented in Table 3.

Table 1: Patient characteristics

Characteristics	Total group (N = 180)	BC group (N = 91)	BBD group (N = 89)	P-value
Sociodemographics				
Age	49.3 ± 10.4	50.7 ± 10.2	47.8 ± 10.6	.067
Living with partner (%)	145 (85.3)	73 (86.9)	72 (83.7)	.563
Children (%)	141 (82.5)	65 (74.7)	76 (87.4)	.053
Educational level				
L [a]	39 (21.8)	18 (19.8)	21 (23.9)	.020*
M [a]	71 (39.7)	29 (31.9)	42 (47.7)	
H [a]	69 (38.5)	44 (48.4)	25 (28.4)	
Salaried work/retirement	136 (81.0)	64 (79.0)	72 (82.8)	.674
Psychological characteristics				
Frequency of complaints about SCF	30.2 ± 10.9	28.7 ± 10.8	31.8 ± 10.9	.060
Fatigue	19.6 ± 5.9	18.4 ± 5.7	20.8 ± 5.8	.007*
High fatigue	54 (30.5)	20 (22.2)	34 (39.1)	.023*
Depressive symptoms	10.2 ± 9.1	11.1 ± 9.1	9.4 ± 9.0	.222
Indication of depression	40 (23.5)	20 (23.8)	20 (23.3)	.932
State anxiety	11.2 ± 3.7	12.2 ± 3.4	10.2 ± 3.7	< .001*
High state anxiety	30 (17.2)	20 (23.0)	10 (11.5)	.071
Trait anxiety	17.4 ± 5.4	17.6 ± 5.4	17.2 ± 5.5	.635
High trait anxiety	30 (17.3)	16 (18.4)	14 (16.3)	.868
Satisfaction with SCF	14.7 ± 2.3	14.8 ± 2.3	14.6 ± 2.4	.637

BBD = Benign breast disease; BC = Breast cancer; SCF = Subjective cognitive functioning

Mean ± standard deviation are presented for age and psychological factors, percentages are between brackets; for the calculation of the percentage missings are not included

[a] L = low education (primary school, lower vocational education); M = middle education (lower general secondary education, intermediate vocational education); H = high education (higher general secondary education, pre-university education, higher vocational education, university)

* $p < .05$

Table 2: Confirmatory Factor Analyses

	CMIN/ DF	p-value	df	χ^2	CFI	NNFI	RMSEA
Wallace et al. [12]/ Wallace [20]	1.839	< .001	247	454.28	.838	.689	.066
Ponds et al. [18]	2.031	< .001	115	233.60	.835	.726	.076
Broadbent et al. [8]	1.967	< .001	275	540.87	.789	.654	.073
Larson et al. [14]/ Matthews et al. [15]	1.817	< .001	251	456.02	.828	.689	.076
Rast et al. [19]	2.0	< .001	183	366.09	.823	.706	.075
Pollina et al. [17]	1.677	< .001	268	449.331	.856	.712	.061
Meiran et al. [16]	1.914	< .001	271	518.617	.804	.668	.071
Wagle et al. [39] Functional sample	2.286	< .001	61	97.5	.823	.731	.085
Wagle et al. [39] Organic sample[a]	1.970	< .001	115	226.5	.854	.748	.073

CFI = Comparative Fit Index; CMIN/DF = minimum discrepancy/degrees of freedom; df = degree of freedom; χ^2 = chi square; NNFI = Non-Normed Fit Index; RMSEA = Root Mean Square Error of Approximation

[a] Item 17 was used in two factors in the original factor structure (factor Cognition/concentration and factor Cognition/memory). In this confirmatory factor analysis this item is only used in the factor Cognition/concentration because the factor loading of this item was higher in this factor.

Table 3: Factor loadings from the rotated factor structure

CFQ items	Factor I Forgetfulness	Factor II Absent-mindedness	Factor III Social recklessness
22. on the tip of your tongue	**.59**		
1. read something without thinking	**.58**		
2. forget why you went from one part of the house to the other	**.58**		
25. think of anything to say	**.57**		
14. wonder if you've used a word correctly	**.53**		
23. forget buy items at shop	**.50**		
20. forget people's names	**.43**		
7. fail to listen to people's names	**.42**		
6. forget turning out light/fire	**.39**		
17. forget where you put something	.31	**.78**	
16. forget appointments		**.58**	
11. leave letters unanswered		**.58**	.42
3. fail notice signposts		**.39**	
8. say something insulting			**.63**
9. fail to hear people speaking when doing something else	.32		**.55**
10. lose temper			**.45**

CFQ = Cognitive Failures Questionnaire

Factor loadings of items belonging to each of the three factors are in bold

Reliability model based on the exploratory factor analysis

Cronbach's alpha coefficients were calculated for the model based on the EFA. The internal consistency of the domains varied: total score CFQ (16 items) (α = .85), Forgetfulness (nine items) (α = .80), Absentmindedness (four items) (α = .74), Social recklessness (three items) (α = .60).

Validity

To measure divergent validity, the scores of the CES-D, and STAI-state were correlated with the total score CFQ (16 items) and the three factors. Pearson's correlations ranged between .08 and .26, indicating small correlations. To measure convergent validity, Pearson's correlations between the total scores and the domains of the CFQ and the FAS and the facet 'cognitive functioning' from the WHOQOL-100 were calculated. These correlations ranged between .30 and -.52 indicating moderate to large correlations. See Table 4 for details.

Table 4: Construct validity of the EFA: Pearson's Correlation Coefficients

	CES-D	STAI-state	FAS	WHOQOL-100 cognitive functioning facet
Total CFQ (16 items)	.26	.24	.46	-.52
Forgetfulness	.25	.24	.40	-.49
Absentmindedness	.20	.19	.35	-.41
Social recklessness	.10	.08	.30	-.31

CES-D = Center for Epidemiological Studies-Depression Scale; CFQ = Cognitive Failures Questionnaire; FAS = Fatigue Assessment Scale STAI-state = State-Trait Anxiety Inventory-State scale; WHOQOL-100 = World Health Organization Quality of Life instrument – 100 items

All correlations are significant at $p < .01$, except correlations of .10 and lower ($p \geq .201$)

Discussion

The aim of this study was to find the best suitable subscales of the CFQ in a population of patients with a breast disease and to examine the psychometric properties. None of the existing models provided an acceptable fit of the factor structure of the CFQ for patients with a breast disease. Therefore, an EFA was done to find the best factorial representation of the CFQ in a population of patients with a breast disease. A three factor solution was found with good psychometric properties. In addition, a total score (16 items) can be calculated which is also reliable and valid. The three factors were Forgetfulness (nine items), Absentmindedness (four items), and Social recklessness (three items). This factor solution accounted for 37% of the variance. This is comparable to most of the other suggested factor solutions by other researchers ranging between 30-36% (e.g., [8, 16, 18]).

However, some exceptions are reported. For instance, Ponds, Boxtel, and Jolles [17] found an explained variance of 49.8%.

The reliability of our three-factor solution was good, although, the internal consistency from one factor fell below the threshold. This could be due to the small number of items within this factor (three items), whereas at least four items are recommended to obtain a Cronbach's alpha level of at least .70 [37].

Our three-factor solution is different from the existing CFQ models. Some similarities exist though. The factor Forgetfulness e.g., is also suggested as a factor by Rast, Zimprich, Van Boxtel, and Jolles [18], but the items in this factor are not completely the same as in our factor. Also, our factor Social recklessness is comparable to the factor Absentmindedness in social situations of Ponds et al. [17], which included only one extra item. Furthermore, our Social recklessness factor (three items) is fully incorporated in the factor Blunders (seven items) from Wallace, Kass, and Stanny [12], and Wallace [19]. Broadbent et al. [8] have stated that self-perceived cognitive failure is a unitary system. Like Rast et al. [18], we have to conclude that it is a composition of different dimensions.

Concerning divergent validity, the factors of the CFQ correlated low with the CES-D and STAI-state. These results are comparable to other studies that examined the correlations between the CFQ (total score of 25 items) and anxiety and depressive symptoms in a population of patients with a breast disease (e.g., Schilder et al. [38]). Convergent validity was shown by moderate to high correlations with the facet Cognitive functioning of the WHOQOL-100. The correlations between the CFQ and the FAS were moderate, suggesting at least an overlap between self-reported problems with SCF and fatigue. This is not surprising since fatigue is one of the predictors of self-reported cognitive functioning [40].

It is important to keep in mind that the CFQ measures the *frequency* of cognitive lapses and not per se the experience of having complaints about SCF. As earlier research showed, the results of the CFQ are not comparable to answers in response to interview questions concerning memory or attention [38]. So, it could be the case that when patients rate their frequency of everyday cognitive failures, they do in fact not experience this as a problem and thus do not complain about it. It could also be the case that the everyday cognitive failures, measured with the CFQ, are not recognized/experienced as cognitive problems. For example, the item 'leave letters unanswered' could be interpreted as 'a normal problem' that exist one's entire life instead of 'cognitive problems'.

A limitation of the present study is the relatively small sample size which made it impossible to run separate factor analyses for the BC patients and the patients with a BBD. This leads to heterogeneity in the study population. However, patients did not score significantly different on the original CFQ (25 items version). In addition, while emotional distress is experienced by BC patients [41], patients with a BBD may also have heightened levels of distress during and after the diagnosis [42, 43]. Our results concerning differences between BC and BBD patients on psychological characteristics are in line with these findings. Concerning depressive symptoms and trait anxiety, no significant differences were found when group means or the percentage of patients scoring high on this variable were compared. Concerning state anxiety, a significant difference in the

group mean was found between BC and BBD patients, but the percentages of patients scoring high on state anxiety did not differ significantly. Furthermore, the aim of future studies is to compare BC patients with BBD patients. Thus, for comparison reasons it is useful to create one factor structure for both groups instead of different structures. Future studies should examine our three-factor solution in separate larger groups of women with BC and BBD to observe if our factor-structure is as stable for both groups as we expect.

Self-report measures are important to understand the patient's perspective on the experienced problems. It is necessary to assess SCF and intervene upon it in clinical practice, because previous research showed that patients do express their concerns regarding these complaints [4, 5]. Until now, the clinical practice is making use of different measures (both validated and non-validated) to examine SCF. The results of the present study show that our three-factor model of the CFQ is the most suitable factorial representation in a population of women with a breast disease, with good reliability and validity. Therefore, it seems an adequate instrument for measuring the frequency of everyday cognitive lapses in women with a breast disease.

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Chapter 4

Chemotherapy and subjective cognitive functioning in patients with breast cancer

Pullens MJJ

De Vries J

Van Warmerdam LJC

Van De Wal MA

Roukema JA

Based on 'Chemotherapy and cognitive complaints in women with breast cancer. Epub ahead of print in Psycho-Oncol.'

Abstract

Background: Results of existing studies are inconclusive concerning the relationship between chemotherapy and subjective cognitive functioning (SCF). The aim of this study was to evaluate SCF of breast cancer (BC) patients and to find predictors of impaired SCF. Both satisfaction and frequency of complaints about SCF were measured.

Methods: BC patients who were about to receive chemotherapy (N = 74) and patients with a benign breast disease (BBD) (N = 63) participated. Before chemotherapy started (Time 1) and three months after ending chemotherapy (and at comparable moments for the BBD group) (Time 2) women completed validated questionnaires concerning the frequency of complaints and satisfaction with SCF, fatigue, perceived stress, anxiety, and depressive symptoms.

Results: No differences were found between the BBD and BC patients concerning the frequency of complaints about SCF across time. Satisfaction with SCF decreased across time in BC patients, but remained stable across time in BBD patients ($p < .001$; $p = .003$ after controlling for state anxiety and perceived stress). Correlations coefficients between the satisfaction and the frequency of complaints about SCF ranged between -.26 to -.49. Depressive symptoms and satisfaction with SCF (Time 1) predicted the frequency of complaints about SCF (Time 2). Diagnosis, frequency of complaints about SCF and state anxiety (Time 1) predicted satisfaction with SCF (Time 2).

Conclusions: BC patients do not differ in the frequency of complaints about SCF compared with BBD patients, but their satisfaction with SCF decreased after treatment. Psychological factors predicted the frequency of complaints about SCF. Psychological factors and diagnosis predicted satisfaction with SCF.

Keywords: cancer, oncology, breast cancer, chemotherapy, subjective cognitive functioning, cognitive complaints

Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women in the developed countries. Because of early detection and the advancements in treatment, the prevalence of BC survivors has increased [1]. Although systemic treatment, such as chemotherapy, improves the clinical outcome of patients with BC, it is also known to have severe side-effects such as complaints about cognitive functioning.

When investigating cognitive functioning, we must make a distinction between objective cognitive functioning (OCF), as measured with standardized neuropsychological tests, and subjective cognitive functioning (SCF), as measured with self-report questionnaires. Problems with SCF refer to the amount of cognitive problems a person experiences in daily life and satisfaction with cognitive functioning [2]. Strong evidence is found for a lack of correlation between OCF and SCF in BC patients [2, 3]. Conflicting results were found regarding the differences in SCF between BC patients and healthy controls [e.g., 4-6] or BC patients with other treatment modalities (e.g., without chemotherapy) [e.g., 6-9]. Furthermore, different periods post-chemotherapy were used (i.e. ranging from six weeks until two years). Also, various measures have been used in assessing SCF in patients with breast problems. Because research regarding the influence of chemotherapy on SCF is scarce and methodologically heterogeneous, it is hard to draw conclusions [2].

In order to identify patients at risk for the development of problems with SCF, it is crucial to examine the existence of sociodemographic, clinical, and psychosocial predictors of SCF. Some studies found that anxiety, depression, psychological distress, trait negative affectivity and fatigue predicted SCF [5, 10, 11]. With a better knowledge about the changes in SCF due to chemotherapy and about the predictors of SCF, we may be able to identify a subgroup of patients who are at risk of experiencing problems with SCF during clinical practice and, as a consequence, are at risk of a reduced quality of life (QoL) [12].

The first aim of this study was to evaluate SCF of BC patients both before and three months after ending chemotherapy in comparison with patients with a benign breast disease (BBD). Because of the heterogeneity in earlier research, both satisfaction and the frequency of complaints about SCF were evaluated. The second aim was to examine the relationship between the frequency of complaints with SCF and the satisfaction with SCF. The third aim was to find predictors of impaired SCF.

Methods

Participants and procedure

Women who were diagnosed with early stage BC and were about to receive chemotherapy between January 2009 and June 2011 in St. Elisabeth hospital (Tilburg), TweeSteden hospital (Tilburg), Maxima Medical Centre (Eindhoven, Veldhoven), Catharina hospital (Eindhoven), St. Anna hospital (Geldrop), Amphia hospital (Breda), and Jeroen Bosch hospital (Den Bosch) were eligible for this study. Women diagnosed with a BBD

were also asked to participate. A cyst, mastopathy or a fibro-adenoma are the most common BBD diagnoses. Treatment of the BBD is not necessary for most women but some women are invited for a follow-up examination several months later. Furthermore, some women want their cyst or fibro-adenoma to be surgically removed.

Women with proven BC recurrence or distant metastases were excluded. Other exclusion criteria were related to the assessment of OCF with neuropsychological tests (these results will be described elsewhere): a history of neuropsychological and/or psychiatric signs or symptoms that lead to deviant neuropsychological test results (e.g., dementia), the use of medication that may lead to deviant neuropsychological results, alcohol and/or drug addiction, and a poor expression in the Dutch language.

BC patients were assessed after surgery, but prior to the start of the first cycle of chemotherapy (Time 1), and three months after ending chemotherapy (Time 2). BBD patients were assessed at equivalent time points. This study was approved by a central medical ethic committee and all local medical ethic committees. All participants provided written informed consent.

Measures

Clinical data were obtained from medical records. Sociodemographic data were obtained from a self-report questionnaire. Furthermore, the following questionnaires were completed, which took approximately 30 minutes:

The Cognitive Failures Questionnaire (CFQ) [13], Dutch version [14] was used to assess self-reported frequency of complaints about SCF. This self-report inventory consists of 25-items. The rating scales range from 0 to 4. A high score indicates more often experienced cognitive failure. A reduced 16-item version of the CFQ was found to assess three factors in women with breast problems: Forgetfulness (e.g., forget why you went from one part of the house to the other, forget to buy items at shop), Absentmindedness (e.g., forget appointments, fail notice signposts), and Social recklessness (e.g., say something insulting, lose temper). The internal consistency, reliability, and validity are reported to be good [Pullens, De Vries, Bogaarts and Roukema, submitted for publication]. To make comparisons with other studies possible, we reported our results with both the original general factor (CFQ 25-items) and the newly developed 16-item version (CFQ-16 items). The Cronbach's alpha coefficients in the current sample are as follows: CFQ-25 item = .88; CFQ-16 item = .83; Forgetfulness = .77; Absentmindedness = .74; Social recklessness = .55.

The cognitive functioning facet of the World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100), Dutch version [15], was used to assess the satisfaction with SCF. The WHOQOL-100 covers 24 facets, assessed by 96 questions, and one General Health and Overall QoL facet. QoL refers to the evaluation of function, e.g., satisfaction with aspects of life. The cognitive functioning facet measures satisfaction with SCF, for example with the following question: 'how satisfied are you with your ability to learn new information?' The rating scales range from 1 to 5. A high score on the cognitive functioning facet indicates satisfaction with SCF. The instrument is reliable and valid [16]

and the sensitivity of the instrument is high [17]. The Cronbach's alpha in the present sample is 0.71

The Center for Epidemiological Studies-Depression Scale (CES-D) [18], Dutch version [19], was used to measure the presence and degree of depressive symptoms. It consists of 20 items. The rating scales range from 0 to 3. A higher score indicates more depressive symptoms. The CES-D is a valid and reliable measure of depressive symptoms in BC patients [20]. The Cronbach's alpha in the present sample is .88.

The Fatigue Assessment Scale (FAS) [21] was used to measure fatigue. It is a 10-item questionnaire that taps fatigue and exhaustion. The response scale is a 5-point scale (1-5). A higher score indicates more symptoms of fatigue. The psychometric properties have been studied in different patient populations, including BC patients, and the validity and reliability are reported to be good [22]. The Cronbach's alpha in the present sample is .85.

The State-Trait Anxiety-state Inventory (STAI) [23], Dutch version [24], was used to measure anxiety. The state scale asks persons how they feel at a particular moment in time, while the trait scale asks people to describe how they generally feel. In this study the shortened 6-item questionnaire for the STAI-state and the 10-item version of the STAI-trait was used. The rating scales range from 1 to 4, a higher score indicates more symptoms of anxiety. The validity and reliability are well established and considered good [24-27]. The Cronbach's alpha in the present sample is .90.

The Perceived Stress Scale-10 (PSS-10) [28] was used as a global measure of perceived stress during the last month. It is the shortened version of the PSS-14 and consists of 10 items, rated on a four-point Likert-scale from 0 to 4. A higher score indicates more perceived stress. The validity and reliability of the PSS are good [30]. The Cronbach's alpha in the present sample is .87.

Statistical procedure

Independent sample t-tests (continuous data) and χ^2-tests (nominal data) were used to examine potential differences between the BC patients and the BBD patients.

General linear model analyses for repeated measures were used to examine the frequency of complaints about SCF (total score, Forgetfulness, Absentmindedness, and Social recklessness) and the satisfaction with SCF across time. Subsequently, these analyses were repeated with variables on which patient groups were different from each other at baseline as covariates. Because of multiple testing, these analyses were corrected with the Bonferroni method (significant at $p < .004$).

Normative samples were used to provide information on when complaints about the satisfaction of and the frequency of complaints about SCF are classified as impaired or not. From a large sample only women were selected and quota sampling was applied to ensure that different age groups were equally represented in the normative samples and the BC group. We defined SCF as impaired if the mean score of the BC group was 1 standard deviation below (satisfaction with SCF) or above (frequency of complaints about SCF) the mean score of the age and gender matched norm group.

Pearson's correlation coefficients between CFQ-25 items, CFQ-16 items, the CFQ subscales and the cognitive functioning facet of the WHOQOL-100 were calculated to

examine the relationship between frequency of complaints about SCF and satisfaction with SCF.

To determine predictors of SCF at Time 2, multivariate regression analyses were conducted. Before the final multivariate regression analyses were run, univariate linear regression analyses with sociodemographic, clinical, and psychological factors at Time 1 as independent variables were performed, aiming at minimizing the number of independent variables in the final multivariate regression analysis. The variables with a $p < .10$ were entered in the final multivariate regression analyses (method: backward). We have chosen for a $p < .10$ instead of $p < .05$ to reduce the risk of excluding a potentially relevant variable [29]. The variable diagnosis was forced in every multivariate regression analysis. Furthermore, because BC patients and BBD patients differed significantly on state anxiety and perceived stress at baseline, effect modifications and confounders were examined for these variables on each dependent variable. A confounder refers to the variable, which influences the found relationship. This can statistically be examined by comparing the beta from the linear regression analysis with and without the variable as a covariate. A difference in the beta value of 10% or more indicates a confounding effect of the variable/covariate [29]. An effect modification is present when different effects are found for different values of a variable, for instance, the found effect is different for patients with or without BC. This can be examined by including the interaction effect in the regression analysis and assessing this p-value [29]. All analyses were performed with the Statistical Package for Social Sciences (SPSS version 18; SPSS Inc., Chicago, IL, USA).

Results

Participants

Of the 213 patients who consented to participate after a phone conversation with the researcher, 23 of them eventually refused to participate because of 'lack of interest' (N = 5), 'lack of time' (N = 4), 'experiencing the study as too burdensome' (N = 3), 'not showing up during appointment' (N = 5), 'experiencing the study subject as too confronting'(N = 3), 'sickness (personal/a family member)' (N = 2), or 'a personal relationship with the researcher' (N = 1). At baseline, 190 women completed the assessments. At the moment of analysis, 137 women completed Time 1 and Time 2; 74 patients with BC and 63 patients with a BBD.

The baseline psychological factors showed a significantly higher score on state anxiety for the BC group ($p < .001$) and perceived stress ($p = .049$). No additional significant differences were found concerning sociodemographic factors and the remaining psychological factors (Table 1).

Table 1: Sociodemographic, clinical, and psychological characteristics

Characteristics	BC group (N = 74)	BBD group (N = 63)	p-value
Sociodemographics			
Age	51.1 ± 9.9	47.8 ± 10.3	.056
Living with partner	59 (79.7)	52 (82.5)	.642
Children	54 (73.0)	54 (85.7)	.206
Education level			
L [a]	15 (20.3)	15 (23.8)	.423
M [a]	25 (33.8)	26 (41.3)	
H [a]	34 (45.9)	22 (34.9)	
Salaried work/retirement	53 (71.3)	53 (84.1)	.609
Psychologist/psychiatric counseling in past	18 (24.3)	14 (22.2)	.638
Clinical characteristics			
Comorbidity [b]	28 (37.8)	28 (44.4)	.325
Type of surgery			
Breast conserving therapy	30 (40.5)		
Mastectomy	44 (59.5)		
Chemotherapy	74 (100)		
Radiotherapy	40 (54.8)		
Hormone therapy	50 (67.6)		
Tumor size			
<1 cm	3 (4.1)		
1-3 cm	52 (71.2)		
>3 cm	18 (24.7)		
Tumor grade [c]			
1	8 (11.4)		
2	32 (45.7)		
3	30 (42.9)		
Axillary lymph node dissection	41 (55.4)		
Psychological characteristics (baseline)			
Trait anxiety	17.7 ± 5.5	16.7 ± 4.7	.269
State anxiety	12.1 ± 3.5	9.7 ± 3.5	< .001*
Depressive symptoms	10.4 ± 8.3	8.4 ± 8.0	.149
Fatigue	18.8 ± 5.7	20.0 ± 5.2	.208
Perceived stress	21.3 ± 5.5	19.6 ± 4.6	.049*

Mean ± standard deviation are presented for age and psychological factors, percentages are between brackets; for the calculation of the percentage missings are not included

BBD = Benign breast disease; BC = Breast cancer

[a] L = low education (primary school, lower vocational education); M = middle education (lower general secondary education, intermediate vocational education); H = high education (higher general secondary education, pre-university education, higher vocational education, university)

[b] Comorbidity consists of heart disease and/or lung disease and/or diabetics and/or neuromuscular disease and/or orthopedic disease

[c] Tumor grade following the Bloom and Richardson grading system for breast cancer

* $p < .05$

Frequency of complaints about subjective cognitive functioning

An effect for time was found on the CFQ-25 items, CFQ-16 items, Forgetfulness and Absentmindedness subscale, indicating that the frequency of complaints about SCF increased across time. After controlling for state anxiety and perceived stress, these effects for time did not remain significant. With regard to the subscale Social recklessness, no significant effects were found. After controlling for state anxiety and perceived stress at Time 1, the results remained the same (Table 2). The mean scores of the BC group on the measures of the frequency of complaints were not more than 1 standard deviation above the mean scores of the norm group, thus the patients were not classified with an impairment on the frequency of complaints about SCF.

Satisfaction with subjective cognitive functioning

An interaction effect was found, indicating that BC patients were less satisfied with their SCF after treatment compared to their satisfaction before the start of the chemotherapy (Table 2 and Figure 1). Satisfaction with SCF in BBD patients did not change across time. After controlling for state anxiety and perceived stress at Time 1, we found that the interaction effect remained significant (Table 2). The mean scores of the BC group were not classified as 'impaired satisfaction with SCF'.

Relationship between frequency of complaints about subjective cognitive functioning and satisfaction with subjective cognitive functioning

Pearson's correlation coefficients between satisfaction with SCF and frequency of complaints about SCF were calculated: satisfaction with SCF correlated significantly with the frequency of complaints about SCF (CFQ 25-items: r = -.49; CFQ 16-items: r = -.47), Forgetfulness (r = -.45), Absentmindedness (r = -.38) and Social recklessness (r = -.26).

Predictors of subjective cognitive functioning

Univariate linear regression analyses revealed that all psychological factors at Time 1 (trait and state anxiety, depressive symptoms, fatigue and perceived stress) predicted the frequency of complaints and satisfaction with SCF. Frequency of complaints about SCF was predicted by satisfaction with SCF and vice versa. These factors, combined with different sociodemographic and clinical variables were included in all final multivariate regression analyses.

Frequency of complaints about SCF (CFQ-25 items, CFQ-16 items) and the subscales Forgetfulness and Absentmindedness were predicted by satisfaction with SCF at Time 1 and depressive symptoms at Time 1, explaining 15.9 to 19.8% of the variance. The CFQ subscale Social recklessness was predicted by satisfaction with SCF at Time 1, depressive symptoms at Time 1 and age, explaining 16.9% of the variance (Table 3).

With regard to satisfaction with SCF, three multivariate linear regression analyses were carried out, one with the CFQ-25 items included as possible predictor, one with the CFQ-16 items included as possible predictor and one with the CFQ subscales included as possible predictors. See Table 3 for significant predictors and beta weights.

Table 2: Mean, standard deviations and the results of the repeated measures analyses of the SCF measures (frequency and satisfaction)

	BBD group		BC group			Without confounders		Corrected for confounders[a]	
	Time 1	Time 2	Time 1	Time 2		P-value	Partial eta squared	P-value	Partial eta squared
Frequency of complaints about SCF									
CFQ-25 items	30.9 ± 9.8	33.8 ± 12.3	29.0 ± 10.5	33.5 ± 14.0	Interaction	.343	.007	.663	.001
					Time	< .001*	.127	.671	.001
					Group	.561	.003	.064	.027
CFQ-16 items	21.3 ± 6.7	23.2 ± 8.5	20.0 ± 7.0	23.4 ± 9.5	Interaction	.163	.014	.401	.005
					Time	< .001*	.153	.566	.003
					Group	.680	.001	.089	.022
CFQ Forgetfulness	13.4 ± 4.3	14.2 ± 4.4	12.5 ± 4.4	14.7 ± 5.6	Interaction	.046*	.030	.153	.016
					Time	< .001*	.127	.851	< .001
					Group	.832	< .001	.119	.019
CFQ Absentmindedness	3.8 ± 2.4	4.7 ± 2.6	3.8 ± 2.1	4.5 ± 2.9	Interaction	.572	.002	.566	.003
					Time	< .001*	.153	.676	.001
					Group	.787	.001	.247	.011
CFQ Social recklessness	3.9 ± 1.5	4.1 ± 1.9	3.4 ± 1.5	4.0 ± 2.2	Interaction	.249	.010	.662	.002
					Time	.035	.033	.274	.009
					Group	.278	.009	.061	.027
Satisfaction with SCF									
WHOQOL-100 Cognitive functioning facet	14.7 ± 2.3	14.6 ± 2.7	14.8 ± 2.2	13.4 ± 2.9	Interaction	< .001*	.086	.003*	.065
					Time	–	–	–	–
					Group	–	–	–	–

BBD = Benign breast disease; BC = Breast cancer; CFQ = Cognitive Failures Questionnaire; WHOQOL-100 = World Health Organization Quality of Life-100 items

[a] confounders are perceived stress and state anxiety at Time 1

* significant at p < .004 (Bonferroni correction)

Table 3: Final multivariate regression analyses for frequency of complaints about SCF and satisfaction with SCF with longitudinal predictors

Dependent variable (measured at Time 2)	Predictors (measured at Time 1)	Beta	p-value	Adjusted R^2	F-value	p-value
Frequency of complaints about SCF						
CFQ-25 items	Satisfaction with SCF	-.268	.004*	.198	16.628	< .001*
	Depressive symptoms	.263	.004*			
CFQ-16 items	Satisfaction with SCF	-.301	.001*	.208	17.627	< .001*
	Depressive symptoms	.242	.008*			
CFQ Forgetfulness	Satisfaction with SCF	-.327	<.001*	.206	17.520	< .001*
	Depressive symptoms	.211	.021*			
CFQ Absentmindedness	Satisfaction with SCF	-.180	.060	.159	9.016	< .001*
	Depressive symptoms	.439	< .001*			
	State anxiety	-.223	.056			
CFQ Social recklessness	Satisfaction with SCF	-.202	.034*	.169	7.252	< .001*
	Depressive symptoms	.240	.014*			
	Comorbidity	-.158	.078			
	Age	-.176	.046*			
Satisfaction with SCF						
WHOQOL-100 Cognitive functioning facet with the CFQ-25 items as one of the predictors	CFQ-25 items	-.403	< .001*	.423	19.630	< .001*
	State anxiety	-.451	< .001*			
	Diagnosis	-.510	.023*			
	Psychologist/psychiatrist counseling in past	-.180	.011*			
	Diagnosis X state anxiety	-.460	.072			
WHOQOL-100 Cognitive functioning facet with the CFQ-16 items as one of the predictors	CFQ-16 items	-.377	< .001*	.428	16.850	< .001*
	Depressive symptoms	-.200	.070			
	State anxiety	-.300	.029*			
	Diagnosis	-.506	.024*			
	Psychologist/psychiatrist counseling in past	-.131	.064			
	Diagnosis X state anxiety	.434	.089			

Table 3: Final multivariate regression analyses for frequency of complaints about SCF and satisfaction with SCF with longitudinal predictors (continued)

Dependent variable (measured at Time 2)	Predictors (measured at Time 1)	Beta	p-value	Adjusted R^2	F-value	p-value
WHOQOL-100 Cognitive functioning facet with the CFQ subscales as possible predictors	CFQ Forgetfulness	-.159	.051	.429	14.640	< .001*
	CFQ Absentmindedness	-.272	.001*			
	State anxiety	-.369	.002*			
	Fatigue	-.161	.078			
	Diagnosis	-.541	.018*			
	Psychologist/psychiatrist counseling in past	-.118	.097			
	Diagnosis X state anxiety	.464	.071			

CFQ = Cognitive Failures Questionnaire; SCF = subjective cognitive functioning; WHOQOL-100 = World Health Organization Quality of Life-100 items
* $p < .05$

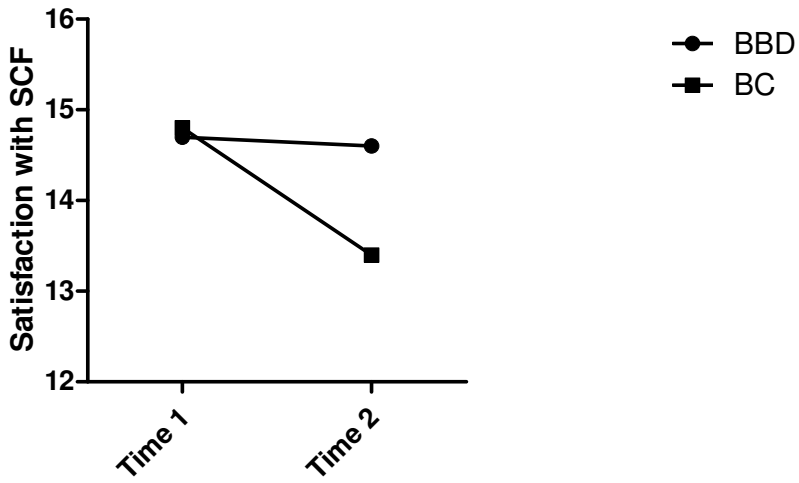

Figure 1: Effect of chemotherapy on satisfaction with subjective cognitive functioning (SCF).
Graph shows the significant interaction effect of time-by-treatment for breast cancer (BC) group.
BBD = Benign breast disease; BC = Breast cancer; SCF = Subjective cognitive functioning

Discussion

The aim of this prospective study was to assess the effect of chemotherapy on frequency and satisfaction with SCF in BC patients compared with women with a BBD and to identify predictors of SCF. This distinction between the two aspects of the definition of SCF (frequency and satisfaction) delivered the interesting finding that even when BC patients and BBD patients report the same frequency of complaints about SCF, satisfaction with SCF decreased across time in BC patients and not in patients with a BBD. This decrease in the satisfaction with SCF in BC patients is also clinically significant: Den Oudsten, Zijlsta and De Vries [submitted for publication] estimated the minimal clinical important difference for BC patients on the WHOQOL-100 to be 1. The mean decrease in satisfaction with SCF was 1.4 for the BC patients in our sample. However, we did find that the mean scores on the satisfaction with SCF stay between the normal range of scores on satisfaction with SCF (on the basis of the norm group).

The discrepancy between the magnitude of the problem (frequency of SCF) and the satisfaction is also seen in other constructs. Concerning social relations, for example, it is known that the size of a person's social network does not represent the satisfaction of that person with his/her social network [30]. A possible explanation of our finding of a decreased satisfaction with SCF in BC patients is that when BC patients for example experience problems with focusing on a text, they can feel extremely bothered by this disability due to the psychological distress they experience during and after the BC

treatment. Another explanation is the growing public awareness of the relationship between cancer treatment and cognition [31].

Schilder et al. also found different patterns for SCF measured with an interview and with the CFQ-25 items in BC patients, but a limitation of this study is that the used interview was non-validated and that the response-scale of this interview was dichotomous (e.g., Do you have complaints with regard to memory? (yes/no)) [32]. This made it impossible to observe a change in gradation of these complaints over time. In the current study satisfaction with SCF is measured with a validated questionnaire and, because of the Likert-scale that has been used, is able to observe change over time within a patient.

Moderate correlations were found between the satisfaction with SCF and the frequency of complaints about SCF and the subscales Forgetfulness and Absentmindedness. This indicates that some overlap not only exists between the two constructs, but also confirms that our approach to SCF (measuring different aspects) is valid.

An association between depressive symptoms and cognitive complaints has often been reported in cancer patients [5, 8, 33]. We found that the frequency of complaints about SCF and its subscales at Time 2 were predicted by satisfaction with SCF and depressive symptoms at Time 1. Social recklessness was also predicted by age. Satisfaction with SCF was predicted by diagnosis, frequency of complaints about SCF (and the subscale Absentmindedness) and state anxiety at Time 1. In one of the regression analyses psychologist/psychiatrist counseling in the past also was a significant predictor of satisfaction with SCF. To our knowledge, this is the first study that examined this relationship. Hermelink et al. found depressive symptoms, together with trait negative affectivity, and chemotherapy as consistent predictors of global problems with SCF as well as specified attention problems experienced in daily life [3]. Other studies found state or trait anxiety as predictors of SCF [33]. Breckenridge et al. found that depressive symptoms, anxiety and fatigue were positively associated with greater perceived cognitive dysfunction [34]. Furthermore, they support our finding that variables concerning demographics and medical/treatment history were not statistically significant for the frequency of SCF. Thus, psychological factors appear to be determinants of SCF. In addition, diagnosis is an important determinant for the satisfaction with SCF, which is reasonable because we found that BC patients, but not the patients with a BBD, decreased in their satisfaction with SCF over time.

The strength of this study is that the frequency of complaints about SCF as well as the satisfaction with SCF is measured with validated questionnaires in patients with breast problems. Our results prove that it is important to make this distinction between the two aspects. Also, contrary to the earlier research [4, 5, 32, 35-37], the version of the CFQ used in the current study is validated in a sample of patients with breast problems. Other strengths are the inclusion of the control group and the longitudinal design with a baseline measurement before the start of chemotherapy. A limitation of this study is the problem with the power to run separate regression analyses for BC patients and BBD patients to identify predictors of SCF. However, by forcing diagnosis in the multivariate regression

analyses, we examined the predictive value of the diagnosis. A significant effect of diagnosis was found concerning only satisfaction with SCF.

In conclusion, BC patients do not differ in the frequency of complaints about SCF compared with BBD patients, but their satisfaction with SCF decreased after chemotherapy. Psychological factors predicted frequency of complaints about SCF. Psychological factors and diagnosis predicted satisfaction with SCF. These findings stress the importance for health care professionals to pay attention to the psychological aspects of the patient. The findings of this study can facilitate health care professionals to identify and support women with breast problems who are at risk for developing a lower satisfaction with SCF.

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Part 2

Objective cognitive functioning

Chapter 5

Chemotherapy and objective cognitive functioning in patients with breast cancer

Pullens MJJ
Roukema JA
Luiten EJT
Van Riel JMGH
De Vries J

Submitted for publication

Abstract

Background: Results of existing studies are inconclusive about objective cognitive functioning (OCF) in breast cancer (BC) patients who are treated with adjuvant chemotherapy. The aims of this study were (i) to evaluate OCF in BC patients, (ii) to examine the effect of anesthesia on OCF, and (iii) to examine the relationship between OCF and subjective cognitive functioning (SCF).

Methods: BC patients who were scheduled to receive adjuvant chemotherapy (N = 58) and a control group of women with a benign breast disease (BBD) (N = 63) participated in the study. Before chemotherapy started and three months after ending chemotherapy (and at comparable moments for the BBD group) women completed validated questionnaires and a neuropsychological test battery. BC patients with neo-adjuvant chemotherapy (N = 13) participated only before the start of chemotherapy.

Results: BC patients showed an impaired course in the domains of verbal memory ($p = .015$) and executive functioning ($p = .042$), compared to BBD patients. With exception from the verbal fluency in professions ($p = .049$), no differences between the BC patients and BBD patients in the percentage of patients who experienced a decrease or an improvement on any neuropsychological measure were found. No specific effect of anesthesia on cognitive functioning was found. Some small to moderate correlations were found between OCF and specific domains of SCF.

Conclusions: Chemotherapy negatively influenced verbal memory and executive functioning in patients with BC. A baseline assessment after surgery seems accurate given that no effect of anesthesia on cognitive functioning was found.

Keywords: cancer, oncology, breast cancer, chemotherapy, objective cognitive functioning, post-operative cognitive dysfunctioning

Introduction

The relationship between systemic cancer treatment and objective cognitive functioning (OCF) has gained increasing interest and was initially studied by cross sectional designs. Since 2004, a number of longitudinal studies were conducted to further unravel this relationship [1]. Whether chemotherapy influences OCF is still inconclusive and prevalence rates vary strongly. These inconclusive results may be due to inconsistencies in study designs as well as methods of analysis. Some studies did not include a control group (e.g., [2-4]). However, in studies in which a control group was included, groups varied from healthy controls (e.g., [5, 6]), to cardiac patients [6], or BC patients treated with hormone therapy or radiotherapy (e.g., [7-9]). Although all studies used neuropsychological tests to measure OCF, there is a large variation in the neuropsychological tests employed and in the definitions used to determine cognitive impairment. Furthermore, timing of cognitive assessments varied between follow-up moments *during* chemotherapy (e.g., [4]) to measurements one or two years later (e.g., [2, 8, 9, 10, 11]).

In sum, there is a need for longitudinal studies with baseline measurements and appropriate control groups. The timing of the baseline measurement often is not standardized in studies designed to analyze OCF in BC patients treated with additional chemotherapy. The first measurement moment of most longitudinal studies in which the effect of adjuvant chemotherapy on OCF is examined takes place *before* chemotherapy, but *after* surgical treatment under general anesthesia. It should be recognized that general anesthesia can affect cognitive functioning, also known as postoperative cognitive dysfunction (POCD) [12].

The aims of the study were (i) to examine OCF *before* and three months *after* adjuvant chemotherapy in comparison with patients with a benign breast disease (BBD). Besides analyses on group level, changes at the individual level were examined too; (ii) to preliminary assess the influence of POCD on OCF in BC patients (for that purpose a group of BC patients receiving neo-adjuvant chemotherapy, i.e., *before* surgery, was included in this study); (iii) to explore the relationship between OCF (measured with neuropsychological tests) and subjective cognitive functioning (SCF) (measured with self-report questionnaires).

Methods

Participants and procedure

Women who were diagnosed with BC and received chemotherapy between January 2009 and August 2011 were eligible for this prospective study. The control group consisted of women diagnosed with a BBD. A cyst, mastopathy or a fibro-adenoma are the most common BBD diagnoses. To examine the effect of POCD on OCF, a group of patients with BC receiving neo-adjuvant chemotherapy was included. Exclusion criteria were defined as: proven loco regional recurrence, distant metastases, a history of neuropsychological and/or psychiatric signs or symptoms that lead to deviant neuropsychological test results

(e.g., dementia), use of medication that may influence neuropsychological results, alcohol and/or drug addiction, and a poor expression in the Dutch language. Patients were recruited by their physician (assistant).

BC patients were assessed prior to initiation of adjuvant chemotherapy (Time 1) and three months following the last cycle of chemotherapy (Time 2). Patients with a BBD were assessed at comparable time points (see Figure 1). BC patients receiving neo-adjuvant chemotherapy were only assessed at Time 1. All participants provided written, informed consent. This study was approved by the central medical ethic committee of the St. Elisabeth hospital (Tilburg) and all the local ethic committees of the participating hospitals.

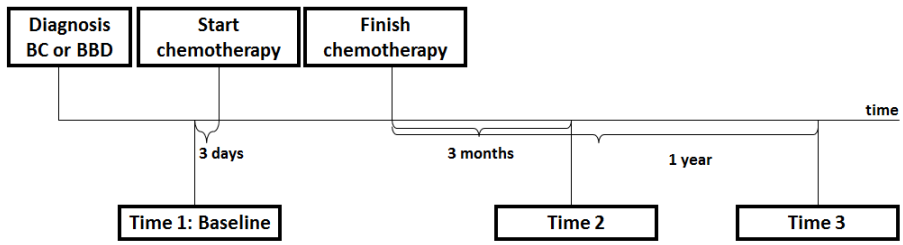

Figure 1: Timeline of the study
BC = Breast cancer; BBD = Benign breast disease

Measurements

Clinical data were obtained from medical records and sociodemographic data were obtained from a self-report questionnaire.

Assessment of neuropsychological performance

A comprehensive test battery, which took approximately 1.5 hours to complete, was designed to assess a broad range of cognitive domains. All tests are widely used in clinical neuropsychological practice and the psychometric properties are well described. Furthermore, the selection of tests was based on previous neuropsychological studies with cancer patients, to enable comparisons of results (e.g., [13, 14]). In addition, the Dutch Adult Reading test provides information on verbal premorbid intelligence [15]. The assessments were conducted either at home or in the hospital.

Attention/processing speed: The Stroop test (card A and B) [16, 17], the Trailmaking test (TMT) A [18], the D2 test [19], the Digit span (forward and backward) and Digit symbol subtest of the Wechsler Adult Intelligence Scale (WAIS) [20], the Fepsy visual reaction test (dominant and non-dominant) and visual searching test [21] were used.

Verbal memory: The Rey auditory verbal learning test (RAVLT) (total recall, delayed recall and recognition) [22, 23] was used.

Visual memory: The visual reproduction subtest of the Wechsler Memory Scale, revised [24] and the Complex figure test (CFT) [25, 26] were used.

Visuospatial functioning: The copy score of the CFT [25, 26] was performed.

Verbal fluency: The Word fluency test (animals and professions) [27] was performed.

Executive functioning: The zoo map test of the Behavioral Assessment of Dysexecutive Syndrome (BADS) (map 1 and map 2) [28], the TMT B [18], the Fepsy binary choice test [21], the Stroop test (card C) [16, 17] were used.

Motor functioning: The Fepsy finger-tapping task (dominant and non-dominant) [21] was used.

Questionnaires

Frequency of complaints about subjective cognitive functioning (SCF) was measured with a reduced 16-item version of the Cognitive Failures Questionnaire (CFQ) [29]. Three factors were assessed: Forgetfulness, Absentmindedness, and Social Recklessness (Pullens, De Vries, Bogaarts and Roukema, submitted for publication). Satisfaction with SCF was measured with the cognitive functioning facet of the World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100) [30]. The Center for Epidemiological Studies-Depression Scale (CES-D) [31] was used to measure depressive symptoms. Fatigue was measured with the Fatigue Assessment Scale (FAS) [32]. The State-Trait Anxiety Inventory (STAI) [33] was used to measure anxiety. In this study the validated shortened 6-item questionnaire for the STAI-state and the 10-item version for the STAI-trait was used [34, 35]. Perceived stress was measured with the Perceived Stress Scale-10 (PSS-10) [36].

Statistical analyses

Independent sample t-tests (continuous data) and χ^2-tests (nominal data) were used to examine potential differences between the BC patients and the BBD patients at Time 1. Furthermore, Mann-Whitney U tests and Fisher exact tests were used to examine differences between (1) participants at Time 1 *and* Time 2 and participants who dropped out of the study, and (2) BC patients receiving adjuvant chemotherapy and neo-adjuvant chemotherapy at Time 1. Fisher exact tests were used to examine differences between patients who decrease and increase on neuropsychological measures.

For analyses on group level, general linear model analyses for repeated measures with age, educational level, perceived stress, state anxiety and fatigue as covariates were used to investigate the course of OCF (with computed cognitive domain scores) across the two assessment points and the differences between the BC and the BBD patients. The cognitive domain scores were computed by first transforming the raw neuropsychological measures to standardized scores (using the BBD patients as reference group) and then computing a mean standardized score for each domain by summing up the standardized scores from the neuropsychological measures, which represent the cognitive domain, and divide this by the number of measures for each cognitive domain. If a significant effect was found for the cognitive domain, subsequently multivariate general linear model analyses for repeated measures were done with the raw neuropsychological measures which represent this cognitive domain.

To identify *individuals* who have shown a significant change in performance across time, a modified version of the Reliable Change Index (RCI) [37] with correction for practice effects was used. The RCI method was defined as ((X2−X1) − (Mbbd2 –

Mbbd1))/SDDbbd, where X1 was the observed score at Time 1, X2 was the observed score at Time 2, SDDbbd was the standard deviation of test–retest difference of BBD patients, Mbbd1 was the mean score at Time 1 of BBD patients, and M2 was the mean score at Time 2 of BBD patients (based on [38]). This approach was applied to each neuropsychological test. Reliable improvement occurred when values exceeded 1.96 and reliable decrease when values fell below −1.96. Scores were recoded so that a lower score at Time 2 indicated a decrease (e.g., the Stroop test indicated a *decrease* instead of an *increase* when scores are higher at Time 2). Performance across variables was summed and patients were classified according to the number of tests on which they significantly decreased (no decrease, decrease on one test, two tests, ≥ three tests).

Pearson correlation coefficients were calculated between the neuropsychological assessments and the measures of SCF (satisfaction and frequency). All analyses were performed with the Statistical Package for Social Sciences (SPSS version 18). For all tests, a p value of <.05 was considered statistically significant (two-sided).

Results

Participants

Of the 213 patients who initially consented to participate by a telephone call from the researcher (MP), 23 of them eventually did not participate because of 'lack of interest' (N = 5), 'lack of time' (N = 4), 'study to burdensome' (N = 3), 'did not show up during appointment' (N = 5), 'study subject to confronting' (N = 3), 'sickness (personal/a family member)' (N = 2), or 'personal relationship with the researcher' (N = 1). At baseline (Time 1), 190 women completed the assessments. At Time 2, seven patients refused to participate because they had lost interest in the study. Furthermore, two patients were excluded because of disease recurrence within three months after the last cycle of chemotherapy (Time 2). Due to the fact that the study was very burdensome and because the main focus of this project is a longer follow-up, we decided not to examine all the patients at Time 2 in order to reduce the number of patients who drop out of the study. The omission of the neuropsychological assessment at Time 2 happened chronologically. A total of 121 women completed both first and second neuropsychological assessment; 58 patients with BC and 63 patients with a BBD.

Concerning the sociodemographic factors, the BC patients were significantly older compared to the BBD patients (see Table 1). The baseline psychological factors showed a significantly higher score on state anxiety and perceived stress for the BC group. Furthermore, patients with a BBD scored higher on fatigue. No additional significant differences were found concerning the remaining psychological factors (see Table 1).

Out of the seven patients who dropped out the study, six had a BBD diagnosis. The drop outs had a significantly lower educational level compared with women who remained in the study (p = .002). There were no significant differences concerning other sociodemographic factors, psychological factors or neuropsychological measures.

Table 1: Sociodemographic, clinical, and psychological characteristics of the participants

Characteristics	BC group (N = 58)	BBD group (N = 63)	P-value
Sociodemographics			
Age	51.7 ± 9.9	47.6 ± 10.0	.024*
Living with partner (%)	44 (84.6)	51 (81.0)	.788
Children (%)	39 (73.6)	55 (87.3)	.101
Educational level			
L [a]	14 (24.1)	26 (41.3)	.111
M [a]	16 (27.6)		
H [a]	28 (48.3)		
Verbal intelligent quotient	80.3 ± 12.6	16 (25.4)	.104
Paid work/retirement	38 (77.6)	21 (33.3)	.675
Psychologist/psychiatric counseling in past	12 (23.1)	76.0 ± 15.7	.926
Clinical characteristics			
Comorbidity[b]	18 (32.1)	22 (36.1)	.801
Type of surgery			
Breast conserving therapy	18 (31.0)		
Mastectomy	40 (69.0)		
Chemotherapy	58 (100)		
Radiotherapy	26 (50.0)		
Tumor size			
1 cm	3 (5.5)		
1-3 cm	40 (72.7)		
>3 cm	12 (21.8)		
Tumor grade[c]			
1	4 (3.3)		
2	25 (20.7)		
3	24 (19.8)		
Axillary lymph node dissection	38 (31.4)		
Psychological characteristics			
CFQ-16 items	19.6 ± 6.2	20.9 ± 6.5	.283
CFQ Forgetfulness	12.5 ± 4.3	13.2 ± 4.5	.443
CFQ Absentmindedness	3.5 ± 2.0	3.9 ± 2.4	.402
CFQ Social recklessness	3.6 ± 1.6	3.9 ± 1.5	.297
Satisfaction with SCF	14.7 ± 2.1	14.6 ± 2.3	.897
Depressive symptoms	10.2 ± 8.3	8.7 ± 8.2	.350
Fatigue	18.3 ± 5.3	20.3 ± 5.6	.047*
Trait anxiety	18.3 ± 5.5	16.7 ± 5.0	.091
State anxiety	12.2 ± 3.3	9.8 ± 3.5	< .001*
Stress	21.8 ± 5.5	20.0 ± 4.7	.050*

BBD = Benign breast disease; BC = Breast cancer; CFQ = Cognitive Failures Questionnaire; SCF = Subjective cognitive functioning

Mean ± standard deviation are presented for age and psychological factors, percentages are between brackets; for the calculation of the percentage missings are not included

[a] L = low education (primary school, lower vocational education); M = middle education (lower general secondary education, intermediate vocational education); H = high education (higher general secondary education, pre-university education, higher vocational education, university)

[b] Comorbidity consists of heart disease and/or lung disease and/or diabetics and/or neuromuscular disease and/or orthopedic disease

[c] Tumor grade following the Bloom and Richardson grading system for breast cancer

* $p < .05$

Group analyses

Neuropsychological test scores (means and standard deviations) at Time 1 and Time 2 are shown in Table 2. After controlling for age, educational level, perceived stress, state anxiety and fatigue at Time 1, three significant effects were found concerning the neuropsychological domains. Both BC patients and BBD patients significantly decreased on the visuospatial functioning ($p = .037$). Furthermore, significant interaction effects in verbal memory ($p = .015$) and in executive functioning ($p = .042$) were found. In both domains BC patients showed a decrease over time while the BBD patients showed a small increase over time.

Evaluating the neuropsychological tests of these significant cognitive domains *separately* revealed significant interaction effects on the RAVLT recall and recognition measure ($p = .041$ and $p = .038$, respectively). Both BC patients and BBD patients increased in the RAVLT recall measure over time, but the BBD patients showed a higher increase compared to the BC patients. On the RAVLT recognition measure, BC patients showed a small decrease over time, in contrast to the BBD patients, who showed a small increase on the RAVLT recognition measure over time. No significant effects were found on the neuropsychological tests which were combined for the cognitive domain of executive functioning.

Individual change analyses

Changes on the individual level are shown in proportions of patients with reliable change (decrease or increase) on every neuropsychological measure in Table 3. With the exception of verbal fluency in professions ($p = .049$), analyses revealed no differences between the BC patients and BBD patients in the percentage of patients who experienced a decrease or an improvement on any neuropsychological measure. Figure 2 shows the percentage of patients who experienced a decrease or an improvement on one, two, or three or more neuropsychological measures stratified by BC patients and BBD patients. There were no significant differences in sociodemographic and psychological factors between patients who showed a decrease on three or more neuropsychological measures and patients with no decrease, or a decrease on one or two neuropsychological measures.

Influence of POCD

Comparisons between BC patients with adjuvant chemotherapy (*after* surgery) and neo-adjuvant chemotherapy ($N = 13$) at Time 1 (baseline) revealed no significant differences concerning sociodemographic factors, psychological factors and neuropsychological measures.

Correlations between OCF and SCF

Baseline mean and standard deviation of the subjective measures of cognitive functioning are shown in Table 1. Pearson correlations between these subjective measures and all the neuropsychological measures in BC patients at Time 1 revealed six small to moderate significant correlations. The Rey recall ($r = .27$), Stroop card C ($r = -.33$), TMT B ($r = -.30$), D2 test ($r = .42$) and Fepsy tapping dominant ($r = .30$) correlated with the factor Social

Recklessness from the CFQ. The professions subtest of the verbal fluency test correlated with the satisfaction with SCF (r = .35).

Table 2: Mean and standard deviation of each neuropsychological test

Neuropsychological measures	BC group		BBD group	
	Time 1	Time 2	Time 1	Time 2
Attention/processing speed				
Stroop card A[a]	43.4 ± 7.9	45.1 ± 9.2	43.1 ± 7.7	44.3 ± 8.4
Stroop card B[a]	54.7 ± 8.7	56.1 ± 9.4	55.2 ± 11.6	54.5 ± 10.4
TMT A[a]	36.6 ± 12.2	35.9 ± 13.0	34.9 ± 14.1	35.6 ± 17.3
D2	408.8 ± 82.0	414.5 ± 80.7	411.3 ± 110.5	430.4 ± 90.4
WAIS digit span	15.6 ± 3.7	16.1 ± 3.8	15.1 ± 3.8	15.4 ± 3.8
WAIS symbol search	74.3 ± 13.3	74.2 ± 16.0	74.2 ± 18.6	75.0 ± 20.3
Fepsy visual reaction dominant hand[a]	308.2 ± 53.0	306.8 ± 52.3	292.1 ± 39.0	299.3 ± 36.3
Fepsy visual reaction non-dominant hand[a]	308.2 ± 53.0	314.5 ± 80.4	302.0 ± 45.1	312.8 ± 44.8
Fepsy visual searching[a]	11.6 ± 3.4	11.8 ± 3.6	11.1 ± 3.3	11.2 ± 3.4
Verbal memory				
RAVLT total recall	48.6 ± 9.4	50.7 ± 8.3	45.7 ± 8.8	50.4 ± 9.4
RAVLT delayed recall	10.2 ± 2.8	10.5 ± 2.5	9.6 ± 2.6	10.8 ± 2.6
RAVLT recognition	29.2 ± 1.2	29.1 ± 1.01	28.9 ± 1.5	29.3 ± 1.2
Visual memory				
WMS	83.7 ± 12.8	83.4 ± 11.5	83.4 ± 13.7	87.2 ± 11.2
CFT delayed recall	17.9 ± 6.0	20.4 ± 5.9	17.1 ± 5.9	19.2 ± 6.6
Visuospatial functioning				
CFT copy	31.7 ± 4.8	31.5 ± 3.4	32.0 ± 2.3	31.4 ± 2.7
Verbal fluency				
Verbal Fluency animals	26.3 ± 5.6	26.7 ± 5.7	26.9 ± 6.2	25.8 ± 6.4
Verbal Fluency professions	19.4 ± 4.9	18.8 ± 4.8	17.9 ± 5.4	18.9 ± 5.7
Executive functioning				
BADS zoo map 1	5.0 ± 3.1	4.6 ± 3.7	3.8 ± 3.6	4.2 ± 3.5
BADS zoo map 2	7.8 ± 0.7	7.3 ± 2.5	7.7 ± 0.9	7.9 ± 0.3
TMT B[a]	77.8 ± 28.8	74.6 ± 34.5	77.6 ± 35.5	70.8 ± 36.4
Fepsy binairy choice[a]	433.1 ± 63.9	445.2 ± 68.9	422.4 ± 62.4	424.2 ± 60.3
Stroop card C[a]	89.1 ± 19.0	86.4 ± 19.8	85.2 ± 22.9	81.3 ± 20.0
Motor functioning				
Fepsy finger tapping dominant hand	62.1 ± 7.5	61.6 ± 8.2	62.9 ± 8.4	61.5 ± 9.2
Fepsy finger tapping non-dominant hand	56.8 ± 7.4	56.1 ± 8.2	58.9 ± 7.8	57.6 ± 8.7

BADS = Behavioral Assessment of Dysexecutive Syndrome; CFT = Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trailmaking Test; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale

[a] A higher score on this test indicates a poorer performance at this test

Table 3: Percentage of each group showing a reliable decrease, increase or no change for each neuropsychological measure

Neuropsychological measures	BC group			BBD group		
	Decrease	Increase	Stable	Decrease	Increase	Stable
Attention/processing speed						
Stroop card A	5.2	1.7	93.1	4.8	1.6	93.7
Stroop card B	5.2	0.0	94.8	3.2	0.0	96.8
TMT A	0.0	0.0	100.0	1.6	0.0	98.4
D2	1.7	0.0	98.3	1.6	3.2	95.2
WAIS digit span	1.7	8.6	89.7	3.2	4.8	92.1
WAIS symbol search	3.4	0.0	96.6	1.6	1.6	96.8
Fepsy visual reaction dominant hand[a]	3.4	12.1	84.5	4.8	1.6	93.7
Fepsy visual reaction non-dominant hand	5.2	3.4	91.4	6.3	3.2	90.5
Fepsy visual searching	5.2	5.2	89.7	3.2	1.6	95.2
Verbal memory						
RAVLT total recall	3.4	5.2	91.4	0.0	4.8	95.2
RAVLT delayed recall	3.4	0.0	96.6	3.2	7.9	88.0
RAVLT recognition	1.7	3.4	94.8	1.6	3.2	95.2
Visual memory						
WMS	0.0	1.9	98.3	3.2	4.8	92.1
CFT delayed recall	1.7	3.4	94.8	1.6	1.6	96.8
Visuospatial functioning						
CFT copy	1.7	5.2	93.1	4.8	0.0	95.2
Verbal fluency						
Verbal Fluency animals	3.4	6.9	89.7	1.6	1.6	96.8
Verbal Fluency professions	5.2	0.0	94.8	0.0	4.8	95.2
Executive functioning						
BADS zoo map 1	1.7	0.0	98.3	1.6	1.6	96.8
BADS zoo map 2	6.9	1.7	91.4	1.6	7.9	90.5
TMT B	3.4	1.7	94.8	1.6	3.2	95.2
Fepsy binairy choice	6.9	1.7	91.4	4.8	1.6	93.7
Stroop card C	1.7	3.4	94.8	3.2	4.8	92.1
Motor functioning						
Fepsy finger tapping dominant hand	1.7	5.2	93.1	3.2	1.6	95.2
Fepsy finger tapping non-dominant hand	5.2	3.4	91.4	1.6	3.2	95.2

BADS = Behavioral Assessment of Dysexecutive Syndrome; CFT = Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trailmaking Test; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale

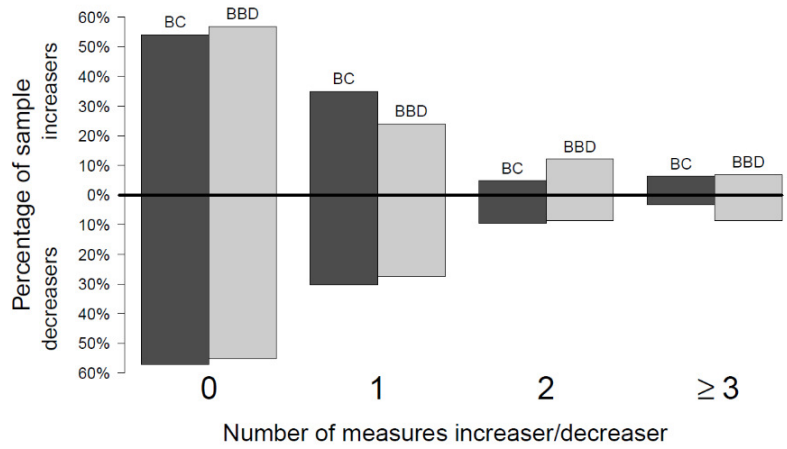

Figure 2: Plot of results Reliable Change Index
BC = Breast cancer; BBD = Benign breast disease

Discussion

The first aim of this prospective study was to examine the effect of chemotherapy on OCF in BC patients compared to patients with a BBD. BC patients showed an impaired verbal memory across time. Quesnel, Savard and Ivers also found a specific negative effect of chemotherapy on verbal memory in BC patients three months after chemotherapy, compared to BC patients who received radiotherapy [39]. In addition, Bender et al. found verbal (working) memory as an affected domain [10]. However, another study did not find effects of treatment on word fluency and memory [40]. We found mixed results concerning executive functioning: separate neuropsychological measures revealed no significant differences, but the created domain score of executive functioning showed a significant interaction effect. Results from the study by Jansen et al. are contrasting with our results concerning executive functioning [4]. They found an improvement in executive functioning over time. Besides the affected domains found in our study, earlier studies reported other affected domains as well, such as working memory [8], visual memory [8], visuospatial functioning [4], processing speed [11, 41], and attention [11]. Studies reporting normal cognitive functioning also exist (e.g., [6, 7, 42, 43]).

Cross-sectional and longitudinal studies have found evidence for cognitive changes due to chemotherapy in a *subgroup* of BC patients (e.g., [3, 9]). We only found a difference on the test verbal fluency in professions between the BC patients and BBD patients in the percentage of patients who experienced a decrease or an improvement on any neuropsychological measure. The difference in verbal fluency is found in some earlier research as well [39, 41, 44] and is in accordance with the clinical practice in which BC

patients often complain of having problems with finding the correct words after they received chemotherapy. Furthermore, we did not find differences in descriptive characteristics between increasers and decreasers on neuropsychological measures.

Earlier prospective studies found cognitive impairments in BC patients at the baseline measurement (after diagnosis before the start of the adjuvant treatment) (e.g., [11, 45]). Therefore it would be interesting to have a baseline measurement before the diagnosis of BC is known. However, this is logistically impossible in clinical practice. Therefore, a baseline measurement after the diagnosis is known is unavoidable. However, nowadays the baseline measurement often takes place after surgery for BC. This study showed no specific effect of anesthesia on cognitive functioning. BC patients with neo-adjuvant chemotherapy did not significantly differ on the neuropsychological measures from the BC patients with adjuvant chemotherapy at Time 1. It is important to notice that our results are preliminary and should be further examined in larger samples of BC patients.

We did not find correlations between OCF and the global measure of the frequency of problems with SCF (measured with the CFQ), but we did find some small to moderate correlations between OCF and the specific domain Social recklessness from the CFQ. Furthermore, a moderate relationship between the satisfaction with SCF and the verbal fluency in professions was found. Independent from the frequency of this complaint, it can disturb patients during daily life if they have word finding problems. Results from earlier research suggest a lack of a relationship between OCF and SCF, but SCF was mostly measured with the global measure in previous studies. The lack of high correlations between OCF and SCF raises the question if the neuropsychological measures are ecologically valid [10, 13, 46]. Because participation is burdensome, it is of great importance to get a better idea of which neuropsychological test actually measure the clinically important changes in OCF in BC patients. Future research should focus on specific domains of SCF when examining the relationship with OCF.

In the current study patients were tested in the hospital *or* at home to improve the inclusion rate and to lower the number of drop outs. Although this study approach corresponds with most other studies in this field, it could be argued that this interferes with the homogeneity in gathering the data. However, we did not find significant differences in neuropsychological functioning between patients being tested at home or in the hospital (data not shown).

A strength of this study is that an intensive neuropsychological test battery was used instead of short screening instruments. In addition, analyses were done on cognitive domains as well as on each neuropsychological test from the significant cognitive domains, and analyses were done both on group level and on an individual level. Furthermore, group analyses were corrected for confounders and the RCI was corrected for practice effects. Other strengths are the longitudinal design with a baseline assessment, the inclusion of a control group, and the relatively low drop-out rate. Collins and MacKenzie [47] stated that it would be useful to have an agreement on a standardized protocol for cancer and cognition studies. This would allow us to establish a large normative database that would provide accurate estimates of reliability and practice effects for a battery of relevant tests.

The longitudinal design and especially the timing of the second measurement three months after the last cycle of chemotherapy are of great value. At this point in life patients pick up their normal daily activities and even sometimes try to recommence work. It is of great interest to have information concerning OCF at this moment, because exactly in this period patients can be confronted with possible disabilities. What would be even more interesting is to examine the course of cognitive functioning not only at this moment in life but over a longer period.

The patients in the control group of this study were BBD patients rather than a healthy control group. We have chosen for BBD patients because they also experienced the emotional and cognitive toll of waiting for the diagnosis that they may have cancer and a subgroup of the BBD's experience stress over and over again because of the follow-up measurements for monitoring the abnormality in the breast. Despite these similarities, BC patients experienced more stress and anxiety at baseline in comparison with BBD patients and patients with a BBD scored higher on fatigue. The analyses on the group level were corrected for these baseline differences.

The number of analyses which were done on the neuropsychological tests increases the chance of a Type 1 error. However, we have chosen for this approach because it was recommended by the International Cognition and Cancer Task Force. With this approach no important information gets lost by only using the created sum scores for the cognitive domains.

In conclusion, the present findings suggest that chemotherapy negatively influenced verbal memory and executive functioning in patients with BC. Furthermore, no differences were found between BC patients and BBD patients in percentages of decreasers on neuropsychological tests (except for verbal fluency). We did not find indications of the existence of POCD. This finding confirms the accuracy of the baseline measurement of OCF *after* surgery and *before* the start of chemotherapy. This is of great importance for future longitudinal studies.

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Chapter 6

Identifying the different courses of cognitive functioning across time in patients with breast cancer treated with chemotherapy

Pullens MJJ
Vermunt JK
Roukema JA
Van Riel JMGH
Roerdink HTJ
De Vries J

Submitted for publication

Abstract

Introduction: Results of existing studies suggest the existence of subgroups within patients with breast cancer (BC) who are treated with chemotherapy with regard to problems with cognitive functioning. Therefore, the aims of this study were to (i) examine cognitive functioning across time in BC patients compared to patients with a benign breast disease (BBD) by evaluating the group means across time, (ii) identify longitudinal development classes for cognitive functioning in BC patients treated with chemotherapy, (iii) describe the sociodemographic and clinical characteristics of the resulting groups, and to compare the groups on their psychological functioning across time.

Methods: BC patients who were scheduled to receive adjuvant chemotherapy (N = 86) and a control group of women with a benign breast disease (BBD) (N = 95) participated in the study. BC patients completed validated questionnaires and a neuropsychological test battery before chemotherapy started, three months and one year after ending chemotherapy (and at comparable moments for the BBD group).

Results: Concerning verbal memory BBD patients stayed stable across time, while it declined in BC patients three months after ending chemotherapy but increased at one year after ending chemotherapy (though they remained below their baseline verbal memory functioning) ($p = .033$). Three longitudinal developmental classes were identified: 'consistently high/average/low cognitive functioning'. This last group had a higher age, lower educational level, and less often salaried work/retirement compared to the other subgroups. Furthermore, they scored worse on state anxiety and depressive symptoms three months after ending chemotherapy compared to the other subgroups.

Conclusion: Verbal memory is affected in BC patients treated with chemotherapy. Three subgroups can be defined within the BC patients: 'consistently high/average/low cognitive functioning'. Further research with a larger sample size is warranted to examine the vulnerability of this last subgroup to develop problems with cognitive functioning after BC treatment.

Keywords: oncology, breast cancer, chemotherapy, objective cognitive functioning, longitudinal development classes

Introduction

The number of long-term breast cancer (BC) survivors is steadily increasing. Therefore, the short-term and long-term side-effects of BC treatment are becoming more important. Over the last decades a growing number of studies have been published that go into the impact of chemotherapy on objective cognitive functioning. Initially, cross-sectional studies showed evidence of cognitive deficits. Recently, longitudinal studies provide further insights into cognitive changes following chemotherapy. The most common affected domains include learning and memory, processing speed and executive function [1]. Most researchers did not find cognitive deficits in all BC patients, but in a smaller proportion of patients, with reports generally ranging between 15 and 50% (e.g., [2-5]).

Cognitive functioning is generally studied by means of prevalence rates or changes in mean scores over time. However, such an approach may mask subgroups of patients with different courses of cognitive functioning over time. Looking into trajectories across time may provide insight in the chronicity of the cognitive problems and may provide more information about the possible subgroups of BC patients with problems concerning cognitive functioning. Knowledge about sociodemographic, clinical and psychological characteristics of the subgroups with different trajectories of cognitive functioning can be helpful in future research concerning the predictors of cognitive deficits after chemotherapy, since this is a topic of ongoing research [6].

Therefore, the first aim of this study was to examine cognitive functioning across time for BC patients compared to patients with a benign breast disease (BBD) by evaluating the group means across time. The second aim was to identify longitudinal development classes for cognitive functioning in BC patients treated with chemotherapy. Thirdly, we aimed to describe the sociodemographic and clinical characteristics of the resulting groups, and to compare the groups on their psychological functioning across time.

Methods

Participants and procedure

Women who were diagnosed with BC and received chemotherapy between January 2009 and August 2011 were eligible for this prospective study. In addition, women diagnosed with a BBD during the same period were also asked to participate in the control group. A cyst, mastopathy or a fibro-adenoma are the most common BBD diagnoses. Women with proven BC recurrence or distant metastases were excluded. Other exclusion criteria were: a history of neuropsychological and/or psychiatric signs or symptoms that lead to deviant neuropsychological test results (e.g., dementia), the use of medication that may influence neuropsychological results, alcohol and/or drug addiction, and a poor expression in the Dutch language. To assess these exclusion criteria, the medical records of all patients were checked.

BC patients were assessed prior to initiation of chemotherapy (Time 1), three months (Time 2) and one year following completion of chemotherapy (Time 3). Patients with a BBD were assessed at equivalent time points. See Figure 1 for the study design. Due to the fact that the study was very burdensome for the participants and because the main focus of this project is at Time 3, we decided not to examine the neuropsychological performance of all patients at Time 2 in order to reduce the number of patients who drop out of the study. The omission of the neuropsychological assessment at Time 2 happened chronologically. All patients did receive the questionnaires at Time 2. All participants provided written, informed consent. This study was approved by the central medical ethic committee of the St. Elisabeth hospital (Tilburg) and all local ethic committees.

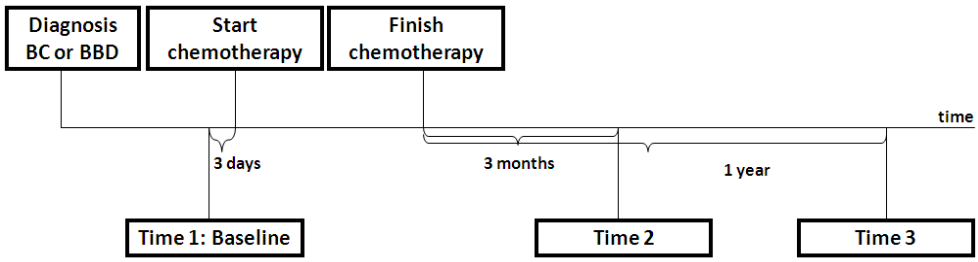

Figure 1: Timeline of the study
BBD = Benign breast disease; BC = Breast cancer

Measurements
Clinical data were obtained from medical records and sociodemographic data were obtained from a self-report questionnaire.

Assessment of neuropsychological performance
A comprehensive test battery, which took approximately 1.5 hours to complete, was designed to assess a broad range of cognitive domains. The battery of 14 neuropsychological tests (comprising 24 test indexes) covered attention, verbal/visual memory, visuospatial functioning, verbal fluency, executive functioning and motor functioning. All tests are widely used in clinical neuropsychological practice and the psychometric properties are well described. Furthermore, the selection of tests was based on previous neuropsychological studies with cancer patients, to enable comparisons of results (e.g., [7, 8]). The assessments were conducted either in the patients' home or in the hospital. Tests were administrated in a fixed order. The neuropsychological tests were scored independently by two persons, after which discrepancies were undone by consensus.

Attention/processing speed: The Stroop test (card A and B) [9, 10], the Trailmaking test (TMT) A [11], the D2 test [12], the Digit span (forward and backward) and Digit symbol subtest of the Wechsler Adult Intelligence Scale (WAIS) [13], the Fepsy visual reaction test (dominant and non-dominant) and visual searching test [14] were used.

Verbal memory: The Rey auditory verbal learning test (RAVLT) (total recall, delayed recall and recognition) [15, 16] was used.

Visual memory: The visual reproduction subtest of the Wechsler Memory Scale, revised [17] and the Complex figure test (CFT) [18, 19] were used.

Visuospatial functioning: The copy score of the CFT [18, 19] was performed.

Verbal fluency: The Word fluency test (animals and professions) [20] was performed.

Executive functioning: The zoo map test of the Behavioral Assessment of Dysexecutive Syndrome (BADS) (map 1 and map 2) [21], the TMT B [11], the Fepsy binary choice test [14], the Stroop test (card C) [9, 10] were used.

Motor functioning: The Fepsy finger-tapping task (dominant and non-dominant) [14] was used.

Questionnaires

Frequency of complaints about subjective cognitive functioning (SCF) was measured with a reduced 16-item version of the Cognitive Failures Questionnaire (CFQ) [22]. Three factors were assessed: Forgetfulness, Absentmindedness, and Social Recklessness (Pullens, De Vries, Bogaarts and Roukema, submitted for publication). Satisfaction with SCF was measured with the cognitive functioning facet of the World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100) [23]. The Center for Epidemiological Studies-Depression Scale (CES-D) [24] was used to measure depressive symptoms. Fatigue was measured with the Fatigue Assessment Scale (FAS) [25]. The State-Trait Anxiety Inventory (STAI) [26] was used to measure anxiety. In this study the validated shortened 6-item questionnaire for the STAI-state and the 10-item version for the STAI-trait were used [27, 28]. Perceived stress was measured with the Perceived Stress Scale-10 (PSS-10) [29].

Statistical analyses

Independent sample t-tests (continuous data) and χ^2-tests (nominal data) were used to examine potential differences between the BC patients and the BBD patients at Time 1. Furthermore, Mann-Whitney U tests and Fisher exact tests were used to examine differences between participants and patients who dropped out of the study at Time 2 and/or Time 3.

The cognitive domain scores were computed by first transforming the raw neuropsychological measures to standardized scores (using the BBD patients as reference group) and then computing a mean standardized score for each domain by summing up the standardized scores from the neuropsychological measures, which represent the cognitive domain, and divide this by the number of measures for each cognitive domain.

In order to examine cognitive functioning across time for BC and BBD patients, repeated measures analysis of variance using general linear mixed modeling analyses were performed, using an unstructured covariance structure. Age, educational level and the variables on which patient groups differed at baseline were used as covariates. In contrast to traditional repeated measures analysis of variance, this method does not automatically exclude every patient from the analysis who has a missing data on a particular moment which preserves the statistical power. Furthermore, this technique is

suitable for analysis of repeated measurements, as it takes into account the possibility of correlated data.

Latent class linear regression analysis, with educational level as covariate, was used to determine the number of latent classes (trajectories) in the course of cognitive functioning (three data waves). The dependent variable was the mean of the scores on the seven separate cognitive domains. Because we were interested in the change over time, time was used as a predictor in the regression model, yielding what is sometimes referred to as a latent class growth model. Models with one to five classes were estimated, using the Bayesian Information Criterion (BIC) for model selection. BIC provides a quantitative index for fit (correspondence between the observed and model predicted responses) taking into account parsimony (number of parameters not being larger than necessary). Based on the results of the selected latent class regression model, each respondent was assigned to the most likely class.

For comparison of sociodemographic, clinical and psychological characteristics between the encountered latent classes, independent sample Mann Whitney U tests and Fisher-exact tests were used. Furthermore, repeated measures analysis of variance using general linear mixed modeling analyses were performed to examine the course of emotional distress (state anxiety, depression, perceived stress, fatigue, SCF (satisfaction and frequency of complaints)) across time for the latent classes. All analyses were performed with the Statistical Package for Social Sciences (SPSS version 19), except for the latent class ordinal regression modeling (Latent Gold 4.5 [30, 31]).

Results

Participants

Of the 213 patients who initially consented to participate after receiving a telephone call from the researcher, 23 of them eventually did not participate because of 'lack of interest' (N = 5), 'lack of time' (N = 4), 'study too burdensome' (N = 3), 'did not show up during appointment' (N = 5), 'study topic too confronting' (N = 3), 'sickness (personal/a family member)' (N = 2), or 'personal relationship with the researcher' (N = 1). At baseline (Time 1), 190 women completed the assessments. Seven patients refused to participate at Time 2 (one BC patient and six BBD patients) and seven patients dropped out of the study at Time 3 (two BC patients and five BBD patients) because they had lost interest in the study. Furthermore, nine patients were excluded because of disease recurrence or metastases during the study. At the moment of the analyses, eight patients still needed to participate at Time 3. The drop outs had a significantly lower educational level compared to women who remained in the study ($p = .039$). Furthermore, the drop outs scored significantly lower on the visual memory domain at Time 1 ($p = .035$). There were no significant differences concerning other sociodemographic factors, psychological factors or neuropsychological measures.

Concerning the sociodemographic factors, the BC patients more often had no children and they had a higher educational level compared to the BBD patients (see

Table 1). The baseline psychological factors showed that BC patients had a significantly higher score on state anxiety, while the BBD patients scored higher on fatigue. No additional significant differences were found between the two groups (see Table 1).

The drop outs had a significantly lower educational level compared to women who remained in the study (p = .039). Furthermore, the drop outs scored significantly lower on the visual memory domain at Time 1 (p = .035). There were no significant differences concerning other sociodemographical factors, psychological factors or neuropsychological measures.

Course of cognitive functioning across time

Concerning visual memory, visuospatial functioning, verbal fluency, attention, executive functioning, and motor functioning no significant effects of time or group were found. Concerning verbal memory, a significant effect of time (p = .007) and a significant interaction effect (p = .033) were found. BBD patients remained stable across time, while verbal memory declined in BC patients three months after ending chemotherapy but increased at one year after ending chemotherapy (though they remained below their baseline verbal memory functioning). In all analyses, diagnosis was not significant. See Figure 2 for the course of the cognitive domain verbal memory across time for BC and BBD patients.

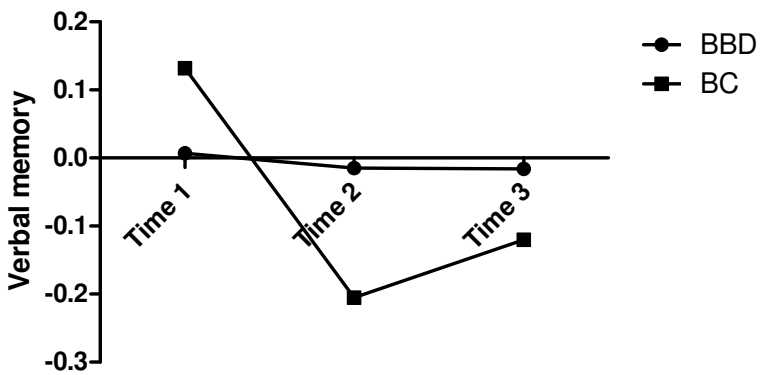

Figure 2: Verbal memory domain across time for BC and BBD patients
BBD = Benign breast disease; BC = Breast cancer

Trajectories of cognitive functioning across time in patients with BC

Based on the BIC we selected the model with thee trajectories for the total score of cognitive functioning for BC patients over the first year after completing chemotherapy. The overall R2 equals 0.76, indicating that the three latent classes describe a large part of the individual differences in the level and change cognitive functioning. The trajectories are visualized in Figure 3 and reflect 'consistently high cognitive functioning', 'consistently average cognitive functioning', and 'consistently low cognitive functioning'. The trajectories contained respectively 40.8, 39.2, and 20.0% of the sample. Moreover, the

estimated proportion of misclassification when assigning individuals to the three classes for further analysis was less that 10%. The most important difference between the three trajectory classes was in the overall level of cognitive functioning (i.e., the intercept) (Wald statistic = 228.84, $p < .001$). The time effect did not significantly differ across classes (Wald statistic = 6.2302, $p = .40$). Although not statistically significant, Figure 3 illustrates that BC patients with the lowest baseline scores show a further decline in their cognitive functioning at Time 2, but recover to their baseline score at Time 3.

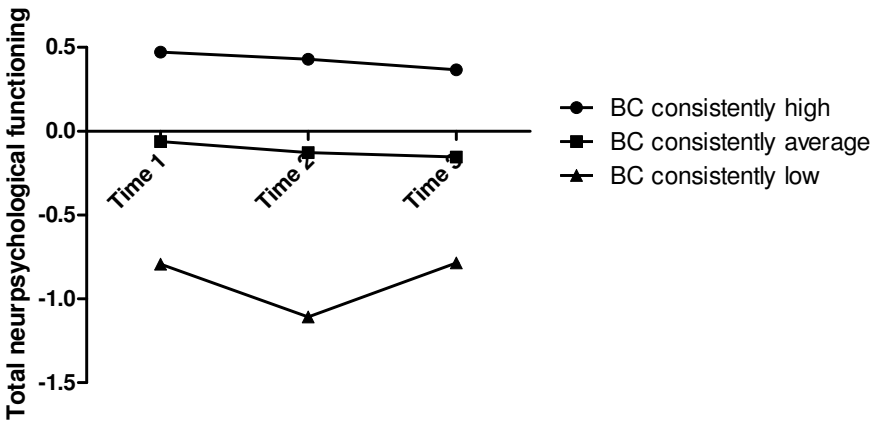

Figure 3: Longitudinal development classes in BC patients
BC = Breast cancer

Characteristics of the three subgroups

A number of significant differences were found in sociodemographic, clinical and psychological characteristics between the three subgroups of BC patients at baseline. The most significant results were found in the subgroup 'consistently low cognitive functioning': their age was significantly higher compared to the other two subgroups, significantly fewer patients had paid work/retirement compared to the other two subgroups, they had the lowest educational level compared to the other two subgroups, and they scored significantly lower on the subscale Social recklessness compared to BC patients with an 'consistently average cognitive functioning' (see Table 1).

Furthermore, the interaction effects of the mixed linear modeling analyses with the different psychological variables as outcome measures were examined to test if these variables significantly differed across time for the three trajectories. The analyses revealed a significant interaction effect for state anxiety ($p = .033$) and depressive symptoms ($p = .047$) at Time 2. BC patients in the group 'consistently low cognitive functioning' increased in their symptoms of state anxiety and depressive symptoms at Time 2 while the other two groups decreased (state anxiety) or increased less (depressive symptoms) at Time 2 compared to Time 1.

Table 1: Sociodemographic, clinical, and psychological characteristics for the complete BC and BBD group and for the 3 subgroups: consistently high cognitive functioning', 'consistently average cognitive functioning', and 'consistently low cognitive functioning'

Characteristics	BC group (N=86)	BBD group (N=95)	p-value	BC consistently high (N = 35)	BC consistently average (N = 34)	BC consistently low (N = 17)	p-value
Sociodemographics							
Age	50.2 ± 9.9	47.8 ± 10.5	.112	49.1 ± 10.5	48.8 ± 9.3	56.9 ± 7.3[d]	.018*
Living with partner	69 (85.2)	80 (87.0)	.737	27 (84.4)	30 (93.8)	10 (76.9)	.235
Children	60 (73.2)	80 (87.9)	.014*	27 (79.4)	21 (65.6)	11 (78.6)	.418
Education level							
L[a]	12 (14.0)	21 (22.1)	.017*	3 (8.8)	0 (0)	9 (60.0)	< .001*
M[a]	29 (33.7)	44 (46.3)		20 (58.8)	7 (20.0)	1 (6.6)	
H[a]	45 (52.3)	30 (31.6)		11 (32.4)	28 (80.0)	5 (33.3)	
Paid work/retirement	61 (81.3)	75 (81.5)	.975	21 (75.0)	31 (93.9)	7 (58.3)	.010*
Psychologist/psychiatric counseling in past	21 (26.3)	24 (26.1)	.981	9 (28.1)	7 (20.6)	4 (33.3)	.569
Clinical characteristics							
Comorbidity[b]	23 (27.7)	30 (33.3)	.423	9 (29.0)	6 (17.1)	7 (46.7)	.104
Type of surgery							
Breast conserving therapy	36 (41.9)			9 (26.5)	18 (51.4)	9 (60.0)	.041*
Mastectomy	50 (58.1)			25 (73.5)	17 (48.6)	6 (40.0)	
Chemotherapy	46 (53.5)			13 (38.2)	22 (62.9)	9 (64.3)	.082
Tumor grade[c]							
1	8 (9.3)			1 (2.9)	3 (8.6)	4 (26.7)	.089
2	41 (47.7)			20 (58.8)	14 (40.0)	6 (40.0)	
3	37 (43.O)			13 (38.2)	18 (51.4)	5 (33.3)	
Axillary lymph node dissection	47 (56.0)			20 (58.8)	19 (55.9)	6 (42.9)	.640

Table 1: Sociodemographic, clinical, and psychological characteristics for the complete BC and BBD group and for the 3 subgroups: consistently high cognitive functioning', 'consistently average cognitive functioning', and 'consistently low cognitive functioning' (continued)

Characteristics	BC group (N=86)	BBD group (N=95)	p-value	BC consistently high (N = 35)	BC consistently average (N = 34)	BC consistently low (N = 17)	p-value
Psychological characteristics (baseline)							
Trait anxiety	17.5 ± 5.2	17.2 ± 5.4	.708	19.1 ± 5.7	16.6 ± 4.3	16.9 ± 5.4	.115
State anxiety	12.1 ± 3.3	10.0 ± 3.7	< .001*	13.0 ± 3.3	11.9 ± 2.7	11.0 ± 4.2	.129
Depressive symptoms	10.5 ± 8.4	9.3 ± 8.7	.359	12.3 ± 8.8	8.8 ± 7.5	11.9 ± 9.6	.236
Fatigue	17.9 ± 5.2	20.6 ± 5.8	.002*	18.5 ± 5.3	17.4 ± 4.2	18.4 ± 7.2	.690
Perceived stress	20.9 ± 5.1	20.0 ± 4.7	.212	22.2 ± 5.7	19.9 ± 4.2	20.6 ± 5.5	.233
Satisfaction with SCF	14.8 ± 2.3	14.6 ± 2.4	.471	14.3 ± 2.6	15.1 ± 2.1	15.3 ± 1.7	.283
Frequency of complaints about SCF (CFQ-25 items)	29.4 ± 10.3	31.6 ± 10.8	.171	30.8 ± 12.0	29.5 ± 8.1	26.5 ± 11.4	.442
Frequency of complaints about SCF (CFQ-16 items)	20.1 ± 6.7	21.6 ± 7.3	.156	21.1 ± 7.9	20.1 ± 5.2	18.0 ± 7.4	.364
Forgetfulness	12.5 ± 4.3	13.4 ± 4.7	.206	13.5 ± 4.6	11.9 ± 3.4	12.2 ± 5.7	.326
Absentmindedness	3.9 ± 2.2	4.2 ± 2.5	.466	4.0 ± 2.3	4.0 ± 2.1	3.3 ± 2.2	.545
Social recklessness	3.6 ± 1.7	4.0 ± 1.7	.067	3.4 ± 1.8	4.2 ± 1.6	2.5 ± 1.3[e]	.006*

BBD = Benign breast disease; BC = Breast cancer; CFQ = Cognitive Failures Questionnaire; SCF = Subjective cognitive functioning; mean ± standard deviation are presented for age and psychological factors, percentages are between brackets; for the calculation of the percentage missings are not included

[a] L= low education (primary school, lower vocational education); M = middle education (lower general secondary education, intermediate vocational education); H = high education (higher general secondary education, pre-university education, higher vocational education, university)

[b] Comorbidity consists of heart disease and/or lung disease and/or diabetics and/or neuromuscular disease and/or orthopedic disease

[c] Tumor grade following the Bloom and Richardson grading system for breast cancer

[d] Significant different from the trajectories 'consistently high cognitive functioning' and 'consistently average cognitive functioning'

[e] Significant different from the trajectory 'consistently average cognitive functioning'

* p < .05

Discussion

This study examined (i) the course of cognitive functioning up to one year after ending chemotherapy in BC patients compared to BBD patients, and (ii) the existence of different trajectories across time within this sample of BC patients. Evaluations of the group means revealed that verbal memory was affected in BC patients three months after ending chemotherapy and partly recovered one year after ending chemotherapy, while BBD patients remained stables across time. Earlier research also found verbal memory as an affected domain after BC treatment (e.g., [32, 33]). While other domains remained stable across time in our study, previous studies also found changes across time in processing speed and executive function in BC patients [1].

As far as we know this is the first study that looked into different trajectories over time in cognitive functioning for BC patients treated with chemotherapy. Three longitudinal development classes were found: 'consistently high cognitive functioning', 'consistently average cognitive functioning', and 'consistently low cognitive functioning'. The overall level of cognitive functioning significantly differed between the three groups. Earlier studies also found pre-treatment cognitive deficits (e.g., [3, 4, 34]). It is unclear whether this pre-treatment cognitive deficit is due to adverse effects of the cancer itself or to other, undefined, factors [35]. It is hypothesized that the adverse effects of cancer(-treatment) manifest themselves in vulnerable individuals. These individuals are most likely to show cognitive changes associated with cancer treatments [35]. The effects of time for the different trajectories on cognitive functioning were not significant in this study. Thus, the development across time concerning cognitive functioning is not significantly different for the three subgroups in this sample. More research, with a larger sample size, is needed to examine if the temporary affected cognitive functioning for the patients in the trajectory 'consistently low cognitive functioning' (which can be observed in Figure 3) is statistically significant and clinically relevant. The characteristics of these potentially vulnerable individuals were found with baseline comparisons between the identified classes. This revealed the interesting finding that the BC patients in the group of 'consistently low cognitive functioning' were significantly older, less educated and had less often salaried work/retirement. The possible vulnerability of older patients with less cognitive reserve is shown in earlier research [36, 37].

Furthermore, concerning psychological factors, this group with 'consistently low cognitive functioning' scored lower on Social recklessness. What's more, changes in state anxiety and depressive symptoms were found. Vearncombe et al. found increased anxiety as a predictor of impairment on two or more cognitive tests in women with BC [38]. Additionally, this study found a significant association between depression at baseline and executive functioning and attention. In contrast, other studies did not find relationships between psychological variables and chemotherapy-induced problems with OCF [39] which demands more research into the relationship between OCF and psychological variables.

Strengths of this study are the prospective design with a baseline assessment and the inclusion of a control group. The patients in the control group of this study were BBD

patients rather than a healthy control group. We have chosen for BBD patients because they also experienced the emotional and cognitive toll of waiting for the possible diagnosis of BC, and a subgroup of the BBD's experienced stress over and over again because of the follow-up measurements for monitoring the abnormality in the breast [40]. Despite these similarities, BC patients experienced more state anxiety at baseline in comparison with BBD patients, while patients with a BBD scored higher on fatigue. The analyses concerning the course of the cognitive domains across time are corrected for these differences. Another strength of this study is the relatively low drop-out rate (3.7% at Time 2; 3.8% at Time 3). We did, however, notice that more patients with a BBD diagnosis dropped out during the study. A possible explanation is that participating in the study is of less importance for these patients because they do not share the worries about the side effects of treatment. Furthermore, patients who dropped out during this study scored significantly lower on visual memory at baseline and had a lower educational level. An additional strength of this study is the relatively large sample size for the analyses across time for all patients with BC treated with chemotherapy, compared to other studies in this field. Jim et al. also used a relatively large sample size [41], but sample sizes of other studies were smaller (e.g., [3, 33, 42-47]).

A limitation of this study is the relatively small subgroup of patients with a 'consistently low cognitive functioning', which may have destabilized the latent classes. The three classes found in this study are a good description of this sample size, however, before we can generalize these findings, these three latent classes need to be replicated in a larger sample. Despite this limitation, the characteristics of these latent classes are useful in clinical practice to signalize patients who can be at risk for developing a decline in their cognitive functioning after treatment with chemotherapy. Another limitation of this study is that not all patients completed the neuropsychological assessment at Time 2. However, for the analyses across time we have used the repeated measures analysis of variance using general linear mixed modeling analyses instead of the traditional repeated measures analysis of variance, so that patients still were included in the analyses when they have a missing data on a particular moment. This preserves the statistical power.

In conclusion, the cognitive domain verbal memory is affected in BC patients treated with chemotherapy. Three subgroups can be defined within the BC patients: 'consistently high, average, and low cognitive functioning'. This last group had a higher age, lower educational level, and less often had salaried work/retirement compared to the other subgroups. More attention is required in clinical practice for a patient with these patient characteristics. More research with a larger sample size is warranted to examine the vulnerability of this subgroup of BC patients to develop problems with cognitive functioning after BC treatment.

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Part 3

Impact of cognitive functioning on quality of life

Chapter 7

The relationship between cognitive functioning and quality of life in patients with breast cancer who receive chemotherapy

Pullens MJJ

Roukema JA

Schepers-van der Sterren EEM

De Vries J

Submitted for publication

Abstract

Purpose: The course of quality of life (QoL) in women with breast cancer (BC) and the impact of objective cognitive functioning (OCF) and subjective cognitive functioning (SCF) on QoL were examined.

Methods: BC patients who were about to receive chemotherapy (N = 86) and patients with a benign breast disease (BBD) (N = 95) participated. Before chemotherapy started (Time 1), three months (Time 2) and one year after ending chemotherapy (and at comparable moments for BBD patients) (Time 3) women completed validated questionnaires and a neuropsychological test battery. General linear mixed modeling analyses and hierarchical regression analyses were used.

Results: BC patients scored significantly lower on Overall QoL and General Health, Physical Health, Psychological Health and Social Relationships at Time 3, compared to BBD patients. SCF and OCF do not add significant variance to the predictive model of QoL. There are indications that the domain of visual memory has a predictive value for Social Relationships.

Conclusion: Overall QoL and General Health, and the Physical Health domain are affected in BC patients one year after ending chemotherapy. Overall, SCF and OCF did not add significant variance to the predictive model for QoL. Further examination of the impact of OCF and SCF on QoL is warranted.

Keywords: breast cancer, quality of life, chemotherapy, objective cognitive functioning, subjective cognitive functioning, cognitive complaints

Introduction

An increasing number of women survive breast cancer (BC). Despite lower mortality rates, BC treatment can also have severe side-effects. Cognitive impairment as a side effect of chemotherapy is a frequently reported concern of BC patients, popularly referred to as 'chemobrain'. An increasing amount of research is focusing on this 'chemobrain'. Problems with cognitive functioning can be measured objectively with neuropsychological tests and subjectively using self-report questionnaires on cognitive complaints. The effects of chemotherapy on cognitive functioning are still inconclusive and prevalence rates vary strongly (e.g., [1-7]).

Because more and more women receive BC treatment such as chemotherapy, the quality of life (QoL) of BC patients has been identified as an end point of great importance in research and clinical practice [8]. Relatively few studies have focused on the impact of problems in cognitive functioning due to chemotherapy on aspects of QoL.

Qualitative studies have found that women can experience cognitive difficulties that affect their functioning at home or their job performance [9-11]. These results underscore the serious ways in which problems with cognitive functioning can affect the life experiences of cancer survivors. Quantitative studies also focused on the association between cognitive functioning and QoL [11-17] or on the predictive value of QoL on cognitive functioning [18]. These studies revealed different results and an association is not always found (e.g., [17, 19]). Besides these studies it is interesting to analyze the clinical significance of cognitive changes in cancer survivors. Reid-Arndt et al. studied neuropsychological functioning and QoL the first year after completing chemotherapy for BC, but they highlighted the preliminary nature of their findings that cognitive difficulties among cancer survivors may be associated with poorer functional outcomes [20]. Further research is needed to validate the potential relationships.

The aims of this prospective follow-up study were (i) to evaluate the course of QoL in BC patients until one year after ending chemotherapy and (ii) to examine the impact of objective cognitive functioning (OCF) and subjective cognitive functioning (SCF) on QoL at one year after ending chemotherapy. Patients with a benign breast disease (BBD) are the control group. Cognitive functioning is associated with emotional distress (e.g., [14, 21-23]), therefore we will not only focus on cognitive functioning, but also take psychological variables into account.

Methods

Participants and procedure

Women who were diagnosed with BC and received chemotherapy between January 2009 and August 2011 were eligible for this prospective longitudinal study. In addition, women diagnosed with a BBP during the same period were also asked to participate in the control group. A cyst, mastopathy or a fibro-adenoma are the most common BBD diagnoses. Women with proven BC recurrence or distant metastases were excluded. Other exclusion

criteria were: a history of neuropsychological and/or psychiatric signs or symptoms that lead to deviant neuropsychological test results (e.g., dementia), the use of medication that may influence neuropsychological results, alcohol and/or drug addiction, and a poor expression in the Dutch language. To assess these exclusion criteria, the medical records of all patients were checked.

BC patients were assessed prior to initiation of chemotherapy (Time 1), three months (Time 2) and one year following completion of chemotherapy (Time 3). Patients with a BBD were assessed at equivalent time points. See Figure 1 for the study design. All participants provided written, informed consent. This study was approved by the central medical ethic committee of the St. Elisabeth hospital (Tilburg) and the local ethic committees of TweeSteden hospital (Tilburg), Maxima Medical Centre (Eindhoven, Veldhoven), Catharina hospital (Eindhoven), St. Anna hospital (Geldrop), Amphia hospital (Breda), and Jeroen Bosch hospital (Den Bosch).

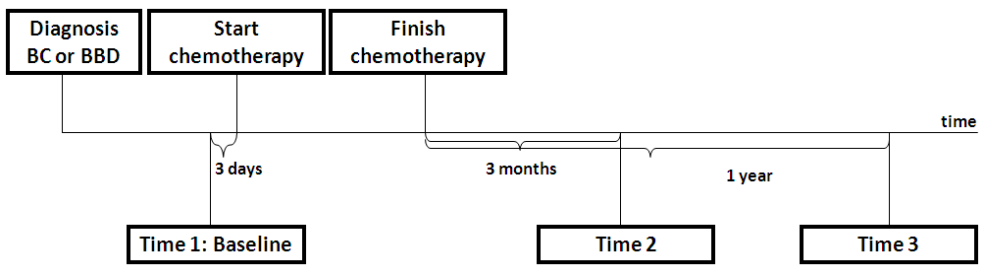

Figure 1: Timeline of the study
BBD = Benign breast disease; BC = Breast cancer

Measures

Clinical data were obtained from medical records and sociodemographic data were obtained from a self-report questionnaire.

Assessment of neuropsychological performance

A comprehensive test battery, which took approximately 1.5 hours to complete, was designed to assess a broad range of cognitive domains. The battery of 14 neuropsychological tests (comprising 24 test indexes), covered attention, verbal-visual memory, visuospatial functioning, verbal fluency, executive functioning, and motor functioning. All tests are widely used in clinical neuropsychological practice and the psychometric properties are well described. Furthermore, the selection of tests was based on previous neuropsychological studies with cancer patients, to make it possible to compare the results (e.g., [24, 25]). A recent review summarized the mostly used neuropsychological tests in the assessment of post-chemotherapy cognitive changes in BC patients. Our selection shows overlap with the tests described in this review [25]. The assessments were conducted either in the patients' home or in the hospital. Tests were administrated in a fixed order. The neuropsychological tests were scored independently by two persons

because of the subjective nature of their scoring. Eventually discrepancies between both scores were solved by reaching consensus. Results from the neuropsychological measures were reported separately and domain scores were calculated.

Attention/processing speed: The Stroop test (card A and B) [26, 27], the Trailmaking test (TMT) A [28], the D2 test [29], the Digit span (forward and backward) and Digit symbol subtest of the Wechsler Adult Intelligence Scale (WAIS) [30], the Fepsy visual reaction test (dominant and non-dominant) and visual searching test [31] were used.

Verbal memory: The Rey auditory verbal learning test (RAVLT) (total recall, delayed recall and recognition) [32, 33] was used.

Visual memory: The visual reproduction subtest of the Wechsler Memory Scale (WMS), revised [34] and the Complex figure test (CFT) [35, 36] were used.

Visuospatial functioning: The copy score of the CFT [35, 36] was performed.

Verbal fluency: The Word fluency test (animals and professions) [37] was performed.

Executive functioning: The zoo map test of the Behavioral Assessment of Dysexecutive Syndrome (BADS) (map 1 and map 2) [38], the TMT B [28], the Fepsy binary choice test [31], the Stroop test (card C) [26, 27] were used.

Motor functioning: The Fepsy finger-tapping task (dominant and non-dominant) [31] was used.

Questionnaires

QoL was measured with the World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100), Dutch version [39]. The WHOQOL-100 is a cross-culturally developed generic multidimensional quality of life questionnaire. It consists of 100 items assessing 24 facets of quality of life and a general facet. These facets can be converted into four domains: Physical, Psychological, Social Relations, and Environment. The response scale is a 5-point scale. The time frame of reference is the previous two weeks. The instrument is reliable and valid [40] and the sensitivity of the instrument is also high [41]. Furthermore it is a reliable and valid instrument to measure QoL in women suspected of having BC [42].

The Cognitive Failures Questionnaire (CFQ) [43], Dutch version [44], was used to assess self-reported frequency of complaints about SCF. This self-report inventory consists of 25-items. The rating scales range from 0 to 4. A high score indicates more often experienced cognitive failure. A reduced 16-item version of the CFQ was found with good psychometric properties [Pullens, De Vries, Bogaarts and Roukema, submitted for publication]. In order to make comparisons with other studies possible, we reported our results with both the original general factor (CFQ 25-items) and the new developed 16-item version (CFQ-16 items).

The cognitive functioning facet of the World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100), Dutch version [39], was used to assess the satisfaction with SCF. A high score on the cognitive functioning facet indicates satisfaction with SCF.

The Center for Epidemiological Studies-Depression Scale (CES-D) [45], Dutch version [46], was used to measure the presence and degree of depressive symptoms. It consists of

20 items, with rating scales range from 0 to 3. A higher score indicates more depressive symptoms. The CES-D is a valid and reliable measure of depressive symptoms in BC patients [47].

The Fatigue Assessment Scale (FAS) [48] was used to measure fatigue. It is a 10-item questionnaire that taps fatigue and exhaustion. The response scale is a 5-point scale (1 to 5). A higher score indicates more symptoms of fatigue. The psychometric properties have been studied in different patient populations, including BC patients, and the validity and reliability are reported to be good [49].

The State-Trait Anxiety Inventory (STAI) [50], Dutch version [51], was used to measure anxiety. The state scale asks persons how they feel at a particular moment in time, while the trait scale asks people to describe how they generally feel. In this study the shortened 6-item questionnaire for the STAI-state [52] and the shortened 10-item version for the STAI-trait [53]. The rating scales range from 1 to 4, a higher score indicates more symptoms of anxiety. The validity and reliability are well established and considered good [51-54].

The Perceived Stress Scale-10 (PSS-10) [55] was used as a global measure of perceived stress during the last month. It is the shortened version of the PSS-14 and consists of ten items, rated on a 4-point Likert-scale from 0 to 4. A higher score indicates more perceived stress. The validity and reliability of the PSS are good [55].

Statistical analyses

Independent sample t-tests (continuous data) and χ^2-tests (nominal data) were used to examine potential differences between the BC patients and the BBD patients at Time 1. Furthermore, Mann-Whitney U tests and Fisher exact tests were used to examine differences between participants and patients who dropped out of the study at Time 2 and/or Time 3.

In order to examine whether BC patients report poorer QoL compared to patients with a BBD, repeated measures analysis of covariance using general linear mixed modeling analyses were performed, using an unstructured covariance structure. Variables on which patient groups were different from each other at baseline were used as covariates. In contrast to traditional repeated measures analysis of variance, this method does not automatically exclude every patient from the analysis who has a missing data on a particular moment. This preserves the statistical power. Furthermore, this technique is suitable for analysis of repeated measurements, as it takes into account the possibility of correlated data.

To determine the predictive value of SCF (Time 1) and OCF (Time 1) on QoL at Time 3 (after controlling for the possible effects of sociodemographic, clinical and psychological variables) hierarchical multiple regression analyses were conducted. For the calculation of the QoL domain Psychological Health the facet 'satisfaction with SCF' was excluded, because this facet was used as a possible predictor in the model. The cognitive domain scores were computed by first transforming the raw neuropsychological measures to standardized scores (using the BBD patients as reference group) and then computing a mean standardized score for each domain by summing up the standardized scores from

the neuropsychological measures, which represent the cognitive domain, and divide this by the number of measures for each cognitive domain. Aiming at minimizing the number of independent control variables in the final hierarchical regression analysis, separate preliminary regression analyses (method: stepwise) were performed with socio-demographic, clinical and psychological variables as independent variables. The variables with a $p < .10$ were entered in the final hierarchical multiple regression analyses (method: Enter). We have chosen for a $p < .10$ instead of $p < .05$ to reduce the risk of excluding a potentially relevant variable. From the clinical variables, only the variable diagnosis was forced in every multivariate regression analysis. Furthermore, because BC patients and BBD patients differed significantly on state anxiety and fatigue at baseline, effect modifications and confounders were examined for these variables on each dependent variable in univariate regression analyses. If a confounding effect was found, the variable was included in the final multivariate regression analysis. Adjusting for these preliminary selected covariates, we composed a five-step model. In step 1, sociodemographic variables were included. Step 2 represented the clinical block with the variable 'diagnosis'. Step 3 included psychological variables. In order to assess the unique association between SCF and QoL, frequency of complaints about SCF (analyses were done separately for CFQ-16 and CFQ-25 items), and satisfaction with SCF were included in step 4. Finally, in order to assess the unique contribution of OCF, step 5 contained the seven OCF domains (attention, verbal memory, visual memory, verbal fluency, visuospatial, executive functioning, and motor functioning). All analyses were performed with the Statistical Package for Social Sciences (SPSS version 19).

Results

Participants

Of the 213 patients who initially consented to participate by a telephone call from the researcher, 23 of them eventually refused to participate because of 'lack of interest' (N = 5), 'lack of time' (N = 4), 'study too burdensome' (N = 3), 'did not show up during appointment' (N = 5), 'study subject too confronting' (N = 3), 'sickness (personal/a family member)' (N = 2), or 'personal relationship with the researcher' (N = 1). At baseline (Time 1), 190 women completed the assessments at Time 1. Seven patients refused to participate at Time 2 (1 BC patient and 6 BBD patients) and seven patients dropped out the study at Time 3 (2 BC patients and 5 BBD patients) because they had lost interest in the study. Furthermore, nine patients were excluded because of disease recurrence or metastases during the study. At the moment of the analyses eight patients still needed to participate at Time 3.

Concerning the sociodemographic factors, the BC patients had significantly more often no children and they had a higher educational level compared to the BBD patients (see Table 1). The baseline psychological factors showed that BC patients had a significantly higher score on state anxiety. Furthermore, patients with a BBD scored higher on fatigue. No additional significant differences were found (see Table 1).

Table 1: Sociodemographic, clinical, and psychological characteristics of the participants

Characteristics	BC group (N = 86)	BBD group (N = 95)	P-value
Sociodemographics			
Age	50.2 ± 9.9	47.8 ± 10.5	.112
Living with partner	69 (85.2)	80 (87.0)	.737
Children	60 (73.2)	80 (87.9)	.014*
Educational level			
L [a]	12 (14.0)	21 (22.1)	.017*
M [a]	29 (33.7)	44 (46.3)	
H [a]	45 (52.3)	30 (31.6)	
Paid work/retirement	61 (81.3)	75 (81.5)	.975
Psychologist/psychiatric counseling in past	12 (23.1)	76.0 ± 15.7	.926
Clinical characteristics			
Comorbidity[b]	23 (27.7)	30 (33.3)	.423
Type of surgery			
Breast conserving therapy	36 (41.9)		
Mastectomy	50 (58.1)		
Chemotherapy	86 (100)		
Radiotherapy	46 (53.5)		
Tumor grade[c]			
1	8 (9.3)		
2	41 (47.7)		
3	37 (43.0)		
Axillary lymph node dissection	47 (56.0)		
Psychological characteristics (baseline)			
Trait anxiety	17.5 ± 5.2	17.2 ± 5.4	.708
State anxiety	12.1 ± 3.3	10.0 ± 3.7	< .001*
Depressive symptoms	10.5 ± 8.4	9.3 ± 8.7	.359
Fatigue	17.9 ± 5.2	20.6 ± 5.8	.002*
Perceived stress	20.9 ± 5.1	20.0 ± 4.7	.212
Satisfaction with SCF	14.8 ± 2.3	14.6 ± 2.4	.471
Frequency of complaints about SCF (CFQ-25 items)	29.4 ± 10.3	31.6 ± 10.8	.171
Frequency of complaints about SCF (CFQ-16 items)	20.1 ± 6.7	21.6 ± 7.3	.156
Forgetfulness	12.5 ± 4.3	13.4 ± 4.7	.206
Absentmindedness	3.9 ± 2.2	4.2 ± 2.5	.466
Social recklessness	3.6 ± 1.7	4.0 ± 1.7	.067

Mean ± standard deviation are presented for age and psychological factors, percentages are between brackets; for the calculation of the percentage missings are not included

BBD = Benign breast disease; BC = Breast cancer; CFQ = Cognitive Failures Questionnaire; SCF = Subjective cognitive functioning

[a] L = low education (primary school, lower vocational education); M = middle education (lower general secondary education, intermediate vocational education); H = high education (higher general secondary education, pre-university education, higher vocational education, university)

[b] Comorbidity consists of heart disease and/or lung disease and/or diabetics and/or neuromuscular disease and/or orthopedic disease

[c] Tumor grade following the Bloom and Richardson grading system for breast cancer

* $p < .05$

The drop outs had a significantly lower educational level compared to women who remained in the study (p = .039). Furthermore, the drop outs scored significantly lower on the visual memory domain at Time 1 (p = .035). There were no significant differences concerning other sociodemographic factors, psychological factors or neuropsychological measures.

Course of quality of life across time

After controlling for fatigue and state anxiety several significant effects were found. A description is given below, but all information is summarized in Table 2 and Figure 2. BBD patients significantly score higher on Overall QoL and General Health, Physical Health, Psychological Health and Social Relationships at Time 3 compared to BC patients. Furthermore, Physical Health is significantly lower for BC patients compared to BBD patients at Time 1. In addition, BC patients score higher on Social Relationships compared to BBD patients at Time 1, but the significant interaction effects reflect a decrease in Social Relationships for BC patients and an increase for BBD patients across time.

Cognitive functioning as predictor of quality of life

The results of these final hierarchical multiple regressions are shown in Table 3. Although beta coefficients, total R Square, R square change, F-values and p-values differed slightly, the same significant results were found for the CFQ-16 and CFQ-25 item version. The R square change of the SCF blocks (Time 1) and the OCF blocks (Time 1) were not statistically significant for the Overall QoL and General Health (Time 3) and for the domains of QoL (Time 3). Thus, the SCF and OCF blocks did not add significant variance to the model. When we look at the beta's of the specific SCF (Time 1) and OCF (Time 1) variables, only visual memory was a significant predictor for Social Relationships (Time 3). See Table 3 for the beta coefficients of the included covariates in the final models.

Table 2: Estimates from mixed linear model (adjusted analyses)[a]

	Overall QoL and General Health	Physical Health	Psychological Health	Social Relationships	Environment
Time 1[b]	-.204	-.780*	279	1.345*	.016
Time 2[b]	.377	-.330	.101	.789*	.125
Diagnosis[c]	.929*	.841*	.539*	1.189*	.112
Interaction Time X diagnosis	F = 1.270; p = .284	F = 2.559; p = .080	F = 1.764; p = .175	F = 10.540; p < .001	F = 4.888; p = .009
Time 1 X diagnosis	-.044	.692*	-.533	-1.768*	-.473
Time 2 X diagnosis	-.445	.513	-.274	-1.486*	-.764*

QoL = Quality of Life

Overall main effects are not given due to the inclusion of interaction effects in the model

[a] Adjusted for fatigue and state anxiety

[b] Time 3 as reference value for BC patients

[c] BC patients as reference value at Time 3

* p ≤ .05

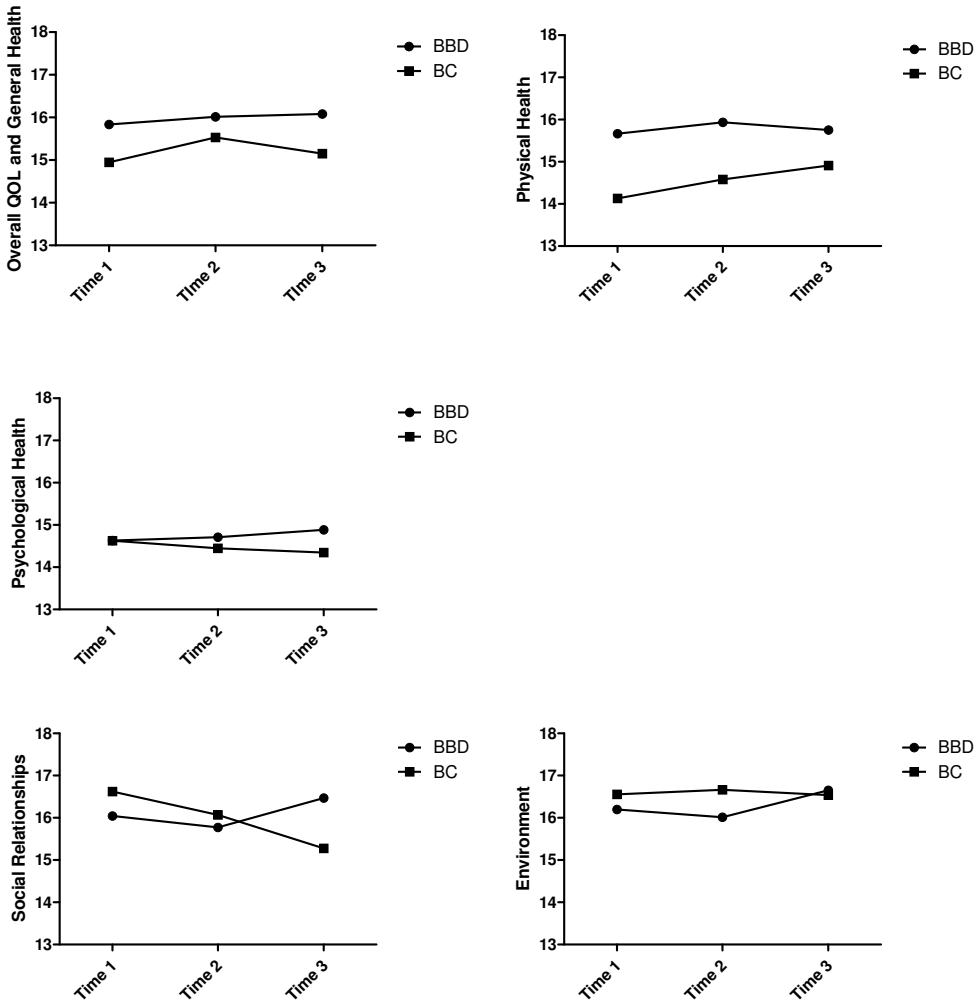

Figure 2: Mean QoL scores on the three measurement moments for Overall QoL and General Health and each domain stratified by diagnosis
BBD = Benign breast disease; BC = Breast cancer; QoL = Quallity of Life

Table 3: Results from the final hierarchical multiple regression analyses of QoL

Dependent variable (measured at Time 3)		Predictors (measured at Time 1)	B[a]		R square		R square change		F-value	
			CFQ-16	CFQ-25	CFQ-16	CFQ-25	CFQ-16	CFQ-25	CFQ-16	CFQ-25
Overall QoL and General Health	Socio-demographic	Partner	.081	.076	.099		.099*		6.566*	
		Paid work	.135	.133						
	Clinical	Diagnosis	-.196*	-.195*	.131		.033*		5.999*	
	Psychological	State anxiety	-.203	-.204	.349		.218*		10.377*	
		Fatigue	-.240*	-.238*						
		Psychologist/psychiatrist counseling in past	-.097	-.096						
	SCF	Frequency of complaints about SCF	.076	.075	.373	.374	.024	.025	8.492*	8.510*
		Satisfaction with SCF	.180	.182						
	OCF	Attention	-.053	-.051	.401		.027		4.769*	4.770*
		Verbal memory	.109	.106						
		Visual memory	.114	.117						
		Verbal fluency	.014	.011						
		Visuospatial	-.133	-.131						
		Executive	.033	.034						
		Motor	.039	.039						
Physical Health	Socio-demographic	Partner	-.012	-.005	.060		.060*		7.660*	
	Clinical	Diagnosis	-.128		.080		.021		5.247*	
	Psychological	Depressive symptoms	-.349*	-.338*	.421		.340*		16.987*	
		State anxiety	-.115	-.121						
		Psychologist/psychiatrist counseling in past	-.246	-.250*						
	SCF	Frequency of complaints about SCF	-.063	-.043	.314		.025	.032	7.450*	7.440*
		Satisfaction with SCF	.157	-.166						

Table 3: Results from the final hierarchical multiple regression analyses of QoL (continued)

Dependent variable (measured at Time 3)		Predictors (measured at Time 1)	B[a]		R square		R square change		F-value	
			CFQ-16	CFQ-25	CFQ-16	CFQ-25	CFQ-16	CFQ-25	CFQ-16	CFQ-25
Physical Health	OCF	Attention	.027	.026	.475	.478	.032	.033	6.984*	7.070*
		Verbal memory	.116	.119						
		Visual memory	.009	.005						
		Verbal fluency	-.016	-.009						
		Visuospatial	-.108	-.111						
		Executive	.117	.118						
		Motor	-.119	-.117						
Psychological Health	Socio-demographic	Partner	.076	.072	.077		.077*		4.976*	
		Children	-.116	-.119						
	Clinical	Diagnosis	-.132*	-.134*	.098		.021		4.307*	
	Psychological	State anxiety	-.085		.608		.510*		29.951*	
		Perceived stress	-.603*	-.604*						
		Psychologist/psychiatrist counseling in past	-.074	-.072						
	SCF	Frequency of complaints about SCF	.072	.059	.622	.621	.014	.013	23.419*	23.356*
		Satisfaction with SCF	.144	.138						
	OCF	Attention	.048	.050	.640	.639	.018	.018	12.666*	12.610*
		Verbal memory	.089	.087						
		Visual memory	.057	.060						
		Verbal fluency	.007	.006						
		Visuospatial	-.099							
		Executive	-.103	-.102						
		Motor	-.039							
Social Relationships	Socio-demographic	Partner	.067	-.073	.103		.103*		6.840*	
		Paid work	.133	.135						
	Clinical	Diagnosis	-.167*	-.166*	.144		.041*		6.625*	

Table 3: Results from the final hierarchical multiple regression analyses of QoL (continued)

Dependent variable (measured at Time 3)		Predictors (measured at Time 1)	B[a]		R square		R square change		F-value	
			CFQ-16	CFQ-25	CFQ-16	CFQ-25	CFQ-16	CFQ-25	CFQ-16	CFQ-25
Social Relationships	Psychological	State anxiety	-.208*	-.209*	.289		.144*	.033		9.410*
		Psychologist/psychiatrist counseling in past	-.210*	-.211*						
	SCF	Frequency of complaints about SCF	-.063	-.043	.314		.025	.032	7.450*	7.440*
		Satisfaction with SCF	.157	-.166						
	OCF	Attention	.149	.146	.370	.369	.056	.055	4.492*	4.466*
		Verbal memory	.030	.032						
		Visual memory	.195*	.192*						
		Verbal fluency	-.036	-.035						
		Visuospatial	-.167							
		Executive	.010	.009						
		Motor	-.104							
Environment	Socio-demographic	Partner	.179	.177	.111		.111*		7.402*	
		Paid work	.191*							
	Clinical	Diagnosis	-.101	-.102	.116		.006		5.182*	
	Psychological	Depressive symptoms	-.202		.182		.066*		6.524*	
	SCF	Frequency of complaints about SCF	-.005	-.007	.196		.014		4.678*	4.673*
		Satisfaction with SCF	.124	.118						
	OCF	Attention	-.032	-.031	.233		.037		2.528*	
		Verbal memory	.061							
		Visual memory	-.006	-.005						
		Verbal fluency	.088							
		Visuospatial	-.081	-.082						
		Executive	.158	.159						
		Motor	-.154	-.153						

B = beta coefficient; CFQ = Cognitive Failures Questionnaire; SCF = subjective cognitive functioning; OCF = objective cognitive functioning

[a] This are the standardized coefficients from the final model in which all variables were entered into the equation

*p < .05

Discussion

In this study the relationship between cognitive functioning (SCF and OCF) and QoL was examined. First, QoL was evaluated across time to examine if QoL was affected in this sample of BC patients. Our specific interest was in patients' QoL one year after ending chemotherapy (Time 3), because the second aim of this study was to examine the predictive value of cognitive functioning (SCF and OCF) on QoL at this measurement. We found that BC patients treated with chemotherapy scored significantly lower on Overall QoL and General Health (Time 3), Physical Health (Time 1 and Time 3), Psychological Health (Time 3) and Social Relationships (Time 3) compared to BBD patients. These results are in line with earlier studies in which patients with chemotherapy scored worse on QoL compared to BC patients treated with local therapy [56], radiotherapy [15] or patients treated without chemotherapy [24].

To better understand the relative impact of cognitive functioning on survivors' well-being, another aim of this study was to assess the unique contribution of cognitive functioning (SCF and OCF) to patients' QoL. We found that SCF and OCF (measured at Time 1) did not add significant variance to the predictive model of QoL at Time 3 (when sociodemographic, clinical, and psychological factors were taken into account). When we looked at the beta coefficients of the various domains of OCF in the final predictive models for QoL we found that visual memory was a significant predictor for Social Relationships at Time 3. This indicates that from the cognitive functioning variables, visual memory may be of importance in the prediction of Social Relationships. However, because the omnibus effect of cognitive functioning did not reach a statistically significant value, this effect of visual memory may only be a sample specific effect which should be verified in other samples.

Our results, in combination with results from earlier research, are inconclusive with regard to the impact of cognitive functioning on QoL [20, 57]. However, evidence exists about the role of neuropsychological measures on *specific aspects* of daily living such as affected productivity at home and at work, problems with returning to work, and affected community integration (e.g., [9, 10, 57-60]). In addition, in clinical practice BC patients continue to report to be bothered by cognitive changes during and after their BC treatment. Thus, the inconsistent findings about the contribution of cognitive functioning (SCF and OCF) to QoL may be explained by the possible weak ecological validity of the SCF and OCF measures [61].

Strengths of this study are the longitudinal design with a baseline assessment, and the relatively low drop-out rate (3.7% at Time 2; 3.8% at Time 3). We did, however, notice that more patients with a BBD diagnosis dropped out during the study. It seems that participating in the study is of less importance to patients who do not have BC. This may be explained by the fact that these patients do not have the worries about side effects of treatment. Furthermore, patients who dropped out during this study scored significantly lower on visual memory at baseline. We cannot explain this finding and we need to take into account that this could be a type 1 error. Another strength of this study is the inclusion of a control group. The patients in the control group of this study were BBD

patients, rather than a healthy control group. We have chosen for BBD patients because they also experienced the emotional and cognitive toll of waiting for the possible diagnosis of BC, and a subgroup of the BBD's experience stress over and over again because of the follow-up measurements for monitoring the abnormality in the breast [62]. Despite these similarities, BC patients experienced more state anxiety at baseline in comparison with BBD patients, and patients with a BBD scored higher on fatigue. The analyses concerning patients' QoL are corrected for these differences. In addition, another strength of this study is that, compared to earlier research concerning the relationship between cognitive functioning and QoL, our sample size is relatively large (e.g., [9, 17, 20]).

A limitation of the study is that the patient population was too small to run separate regression analyses for the BC and BBD patients. Diagnosis turned out to be a significant predictor for Overall QoL and General Health, Physical Health and Social Relationships. However, the aim of these regression analyses was to find the predictive value of OCF and SCF on QoL. Therefore we think that this could be examined in a good way in patients with a breast disease (benign and malignant) to preserve power of the analyses. In this way we were able to include more variables in the predictive model to examine the impact of cognitive functioning (OCF and SCF) on QoL, taking into account the effects of emotional distress, sociodemographic and clinical variables. More research, with larger sample sizes are needed to test the predictive value of cognitive functioning (OCF and SCF) on QoL and to test if our found effect of visual memory on Social Relationships was a sample specific effect or can be generalized.

In conclusion, compared to BBD patients, Overall QoL and General Health and the Physical Health domain are affected in BC patients one year after ending chemotherapy. Overall, SCF and OCF (measured at Time 1) did not add significant variance to the predictive model for QoL (measured at Time 3). There are indications that the specific OCF domain visual memory has a predictive value for Social Relationships. Further examination of the impact of this domain on QoL is warranted. Indentifying risk factors is of great importance because this can lead to interventions that could reduce the impact of cancer and its treatment on cognitive functioning and QoL.

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Chapter 8

Summary and general discussion

Cognitive functioning (subjective cognitive functioning (SCF) and objective cognitive functioning (OCF)) in patients with breast cancer (BC) who were treated with chemotherapy was examined in this thesis. Furthermore, the relationship between cognitive functioning (SCF and OCF) and quality of life (QoL) was examined. This chapter consists of a summary and interpretation of the main findings of the studies that have been presented. Subsequently, methodological considerations, suggestions for future research, and clinical implications that follow from these studies will be given.

Summary and interpretation of main findings

Subjective cognitive functioning

When this study started, at the end of 2008, the literature about the effects of chemotherapy on cognitive functioning was emerging. However, most research focused on the effects of chemotherapy on OCF. At that moment, several meta-analyses were written (e.g., [1-4]) and an international working group (The International Cognition and Cancer Task Force (ICCTF)) met each other several times [5-7]. However, the effects of chemotherapy on SCF were not examined thoroughly and there were no articles available which provided an overview of this topic. Therefore, we performed a systematic review of the literature to investigate the effects of adjuvant treatment for BC on SCF (**Chapter 2**). The reported prevalence of problems with SCF appeared to vary considerably, which is most likely the result of the variety in definitions, questionnaires, and cut-off scores. Problems with SCF do exist in the BC population, but it is unclear if these problems are more commonly found among patients with BC than in the general population. No differences were found in the prevalence of problems with SCF between pre- and post-treatment assessments, which implies that there is no effect of systemic treatment on the occurrence of problems with SCF. However, evidence was found for short time increased *severity* of problems with SCF directly after systemic treatment, compared to the baseline assessment. Fluctuating results were found for the changes in severity and occurrence of problems with SCF across time after treatment.

Another finding was the inconsistent way in which SCF was measured across studies. Different ad-hoc semi-structured interviews and a number of self-report questionnaires were used to determine SCF. One of the used questionnaires was the Cognitive Failures Questionnaire (CFQ) (25 items) [8]. Because the CFQ shows a different factor structure in different diseases, the factor structure and psychometric properties of the questionnaire have been examined in **Chapter 3**. None of the existing models met the criteria for an acceptable fit in the confirmatory factor analyses. Therefore, an exploratory factor analysis was done to find the best factorial representation of the CFQ in a population of patients with a breast disease. A three factor solution with good psychometric properties was found. The three factors were Forgetfulness (nine items), Absentmindedness (four items), and Social recklessness (three items). This factor solution accounted for 37% of the variance. Concerning divergent validity, the factors of the CFQ correlated low with depressive symptoms and state anxiety. The new three-factor model showed good

reliability and validity. Convergent validity was shown by moderate to high correlations with satisfaction with SCF. The correlations between the CFQ and fatigue were moderate, suggesting at least an overlap between self-reported problems with SCF and fatigue. The results of the present study show that our three-factor model of the CFQ is the most suitable factorial representation in a population of women with a breast disease, with good reliability and validity. Therefore, it seems an adequate instrument for measuring the frequency of everyday cognitive lapses in women with a breast disease.

Chapter 2 also described several shortcomings in the available studies concerning SCF: The cross-sectional nature of many existing studies limits conclusions about causality and the development of SCF over time. Furthermore, the lack of baseline measurements problematized inferences regarding a real increase of problems with SCF after systemic treatment. Other shortcomings were the small patient populations, lack of control groups, and lack of controlling for confounding variables. In order to overcome these issues **Chapter 4** described the results of a prospective study, with a control group and a baseline assessment, concerning SCF in BC patients who are treated with chemotherapy. Both satisfaction (with a facet from the WHOQOL-100) and frequency of complaints (with the CFQ-16 items) about SCF were measured before the start of chemotherapy and three months after ending chemotherapy. Patients with BC did not differ in the frequency of complaints about SCF compared to patients with a benign breast disease (BBD), but their satisfaction with SCF was decreased three months after ending chemotherapy. This decrease in the satisfaction with SCF in patients with BC was also clinically relevant. Furthermore, the mean scores of satisfaction with SCF stayed within the normal range of scores at both times of measurement (based on data from a large norm population). Psychological factors (especially depressive symptoms and state anxiety) predicted the frequency of complaints about SCF. Psychological factors, diagnosis (benign/malign), as well as prior counselling by a psychologist or psychiatrist predicted satisfaction with SCF. As far as we know, this was the first study that examined the role of prior counseling in emotional distress on SCF and it turned out that earlier emotional distress was an important predictor of SCF.

Thus, the review showed that the severity of problems with SCF shortly increased directly after treatment. Our own study found that the satisfaction with SCF decreased three months after ending chemotherapy in BC patients. Despite the finding that the problems stay within the normal range, the statistically and clinically relevant *decrease* in satisfaction with SCF across time needs to be taken seriously.

Objective cognitive functioning

Chapter 5 examined the effect of chemotherapy on OCF (i.e., different cognitive domains and the separate neuropsychological tests) in BC patients compared to patients with a BBD before and three months after ending chemotherapy (and at comparable moments for the patients with a BBD). BC patients showed an impaired verbal memory across time compared to BBD patients. We found mixed results concerning executive functioning: the separate neuropsychological measures revealed no significant differences concerning time or group, but the created domain score of executive functioning showed a significant

interaction effect between BC and BBD patients. Earlier studies reported other affected domains as well, such as working memory [9], visual memory [9], visuospatial functioning [10], processing speed [11, 12], and attention [12]. There are also studies reporting normal cognitive functioning (e.g., [13-16]), or even improvements in cognitive functioning [10]. Furthermore, we only found a difference on the test verbal fluency in professions between the BC patients and BBD patients in the percentage of patients who experienced a decrease or an improvement on any neuropsychological measure. The difference in verbal fluency is found in some earlier research as well [11, 17, 18], and is in accordance with clinical practice in which BC patients who received chemotherapy often complain of having problems with finding the correct words. In addition, a Reliable Change Index with a correction for practice effects [19] was used to identify individuals with a significant change over time in patient with BC or a BBD. We did not find differences socio-demographical and psychological factors between patients who showed a decrease on three or more neuropsychological measures and patients with no decrease, or a decrease on one or two neuropsychological measures.

The aim of **Chapter 6** was to examine the course of OCF up to one year after ending chemotherapy in BC patients compared to BBD patients as well as to examine the existence of different longitudinal trajectories within this sample of BC patients. Verbal memory was decreased in BC patients one year after treatment while it stayed stable in patients with a BBD. Three longitudinal development classes were found within the patients with BC: 'consistently high cognitive functioning', 'consistently average cognitive functioning', and 'consistently low cognitive functioning'. BC patients in this last group were significantly older, less educated, and less often had paid work (or had paid work in the past and are with retirement at this moment). The possible vulnerability of older patients with less cognitive reserve is shown in earlier research [11, 20].

Thus, concerning OCF we can conclude that verbal memory was affected three months and one year after ending chemotherapy in patients with BC compared to patients with a BBD. Executive functioning (at the domain level) was affected three months after ending chemotherapy in BC patients while patients with a BBD showed a small increase across time. Furthermore, we can distinguish three longitudinal developmental classes within the patient with BC. It needs to be further examined if the patients in the 'consistently low cognitive functioning' group are the individuals who are vulnerable for the adverse effects of cancer treatment.

Relationship between subjective and objective cognitive functioning

In Chapter 2 and Chapter 5 of this thesis, the relationship between SCF and OCF was examined. Strong evidence was found in Chapter 2 (systematic review) for a lack of a relationship. There are a number of possible explanations for the absence of this relationship. First, the neuropsychological tests may be insufficiently sensitive to detect mild problems with OCF in patients treated for cancer, because these tests are routinely used in groups of patients with degenerative decline in cognitive functioning (e.g., Alzheimer) or other brain injuries [5, 21]. In addition, the goal of neuropsychological assessments is to obtain participants' best performance, thus environmental factors which

are known to reduce cognitive functioning are minimized during the assessment [22]. It is questionable if this specific test-situation provides relevant information about the performance in everyday life and is able to detect subtle cognitive impairments [5, 23, 24]. The discrepancy in the time frame could be a second explanation: objective tests evaluate performance at a point in time, whereas self-report encompasses assessment of performance over a broader period (e.g., 'the last two weeks') [5]. Third, increased knowledge about the relationship between chemotherapy and cognitive dysfunction could influence the expression of problems with SCF [25]. Fourth, subjective measures and neuropsychological tests do not measure the same construct. Objective performance on tests may not accurately reflect the problems with SCF that many women experience after treatment of BC. Alternatively, reported problems with SCF may indicate emotional distress instead of real cognitive problems and is a reaction of a patient to stressful events [26]. This correlation between SCF and emotional distress has also been observed in other populations (e.g. epilepsy patients or patients with multiple sclerosis [27, 28]. Fifth, OCF and SCF possibly are not measured specific enough: in the studies included in Chapter 2 SCF was measured with a global scale [26, 29]. In line with the previous studies, no correlations were found in Chapter 5 between OCF and the global measure of the frequency of problems with SCF (measured with the CFQ). However, we did find some small to moderate correlations between specific neuropsychological tests (Rey recall [30], Stroop [31], Trail Making Test B [32], D2-test [33], Fepsy tapping dominant [34]) and specific domains of SCF (Social recklessness). It seemed that there might be a small to moderate relationship between OCF and SCF, when SCF is measured with more specific outcome measures. The assessment of specific problems with SCF seems to be fruitful in other patient populations as well (e.g., in predicting preclinical Alzheimer's disease [35]).

Impact of cognitive functioning on quality of life

To better understand the relative impact of cognitive functioning on survivors' well-being, the aim of **Chapter 7** was to assess the unique contribution of cognitive functioning (SCF and OCF) to patients' QoL. Compared to BBD patients, Overall QoL and General Health, and the Physical Health domain are affected in BC patients one year after ending chemotherapy. Overall, cognitive functioning (SCF and OCF) did not add significant variance to the predictive model for QoL (when sociodemographical, medical, and psychological variables were taken into account). Our results, in combination with results from earlier research, are inconsistent with regard to the impact of cognitive functioning on QoL [36, 37]. However, evidence exists about the role of neuropsychological measures on aspects related to QoL, i.e. aspects of daily living, such as affected productivity at home and at work, problems with returning to work, and affected community integration (e.g., [36, 38-42]. In addition, in clinical practice BC patients continue to report to be bothered by cognitive changes during and after their BC treatment.

Methodological considerations

Considerations with regard to the study design

Cognitive functioning and patient-reported outcomes

An important strength of this thesis is that it provides insight in the chemobrain in patients with BC by examining both SCF and OCF. An additional strength of this thesis is that both the frequency of complaints about SCF and satisfaction with SCF were measured. This is unique and delivered interesting findings.

Furthermore, this thesis used a broad neuropsychological assessment as opposed to quick screening tests (such as the Mini-Mental State Examination [43]). The test selection of this thesis was based on the psychometric properties of the tests and on earlier research (e.g., [44, 45]) which enabled the comparison of results. The division of these tests in the cognitive domains was based on recommendations [46], experience in clinical practice, and earlier research. However, we need to stress that the selected neuropsychological tests and the division of these tests into different domains are heterogeneous in the available literature. Another division of the neuropsychological tests may deliver some other results. In 2011, the ICCTF published their recommendations concerning the selection of neuropsychological tests and cognitive domains [7]. They recommend using neuropsychological measures that assess cognitive functioning from the following cognitive domains which are related to a frontal sub-cortical profile: learning and memory, processing speed and executive functioning. The broad neuropsychological assessment in this thesis covers these aspects and included other domains as well.

This thesis did not only focus on measures of cognitive functioning (SCF and OCF); other patient-reported outcomes were also taken into account. Besides the demographical and clinical characteristics, these patient-reported outcomes provide a more complete picture of the patient. In addition, because of the associations between anxiety, depression, fatigue and stress with cognitive functioning (SCF and OCF) [24], these psychological variables are important confounders for the effects of chemotherapy on cognitive functioning. Moreover, especially depressive symptoms and state anxiety are predictors of problems with SCF.

Prospective design and inclusion of a control group

The prospective design of this study included a baseline measurement of cognitive functioning, which made it possible to evaluate cognitive functioning of BC patients after surgery, but prior to the start of chemotherapy. However, baseline scores may be confounded by symptoms of emotional distress (such as anxiety/depressive symptoms) due to the diagnosis of BC [29].

Because of the inclusion of a control group in this study, we were able to examine the role of psychological distress on cognitive functioning at baseline in both groups. Psychological variables on which the groups differed significantly at baseline were used as covariates in the analyses. The patients in the control group of this study were BBD patients, rather than a healthy control group. We have chosen for BBD patients because they also experienced the emotional and cognitive toll of waiting for the diagnosis that

may have been cancer. In addition, a subgroup of the BBD's experience stress over and over again because of the follow-up measurements for monitoring the abnormality in the breast [47]. Furthermore, besides the possible effect of psychological distress on cognitive functioning, it is hypothesized that cognitive functioning measured at baseline also can be affected by the anesthesia which was necessary for the surgery, also known as post-operative cognitive dysfunctioning (POCD) [48]. This possible effect of POCD was examined in Chapter 5 by comparing BC patients scheduled for adjuvant chemotherapy (after the surgery) with BC patients scheduled for neo-adjuvant chemotherapy (before the surgery). We did not find significant differences on the neuropsychological measures at baseline.

In sum, the timing of the baseline measurement seemed not to be of influence on OCF and because of the comparisons with the control group at baseline, we were able to control for the influence of psychological variables on cognitive functioning.

Considerations concerning study procedure

Participants

Because this study was very burdensome for the patient as well as the physician or the nurse practitioner who provided the first information about this study to the patient, there was a potential loss of eligible patients. We do not know if these samples of BC and BBD patients are representative for the whole BC and BBD populations. A possibility is that more patients who actually do experience complaints about SCF and/or OCF are more interested in participating in this study. This can lead to an overestimation of the results. On the other hand, some reasons for not participating in the study (10.8% refused to participate after they initially consented to participate) were that the study was too burdensome or that the study subject was too confronting, which can lead to an underestimation of the problems observed in the current studies.

Patients included in this study knew that the objective of this study was to examine problems with cognitive functioning after chemotherapy. As a researcher I always emphasized that we do not know *if* there are effects and that this is the reason for this study. Despite this effort, participants may have been predisposed to pre-existing knowledge about chemobrain [49]. This may result in an overestimation of the problems observed in the current studies.

The studies in this thesis had a relatively low drop-out rate (3.7% at Time 2; 3.8% at Time 3). We did, however, notice that the loss to follow-up was not completely random, as more patients with a BBD than a BC diagnosis dropped out during the study. This may be explained by the fact that these patients do not have to worry about the side effects of any treatment. Furthermore, patients who dropped out at Time 3 scored significantly lower on visual memory at baseline and had a lower educational level.

Procedure of neuropsychological assessment

In the current study patients were tested at home or in the participating hospitals. Secondary analyses showed no differences in the performance on neuropsychological tests between patients tested at home and patients tested in the hospital. Thus, it seemed

that the location of the neuropsychological assessments did not influence the performance on these tasks.

Due to the burdensome of the study for the patients and due to insufficient resources to examine the neuropsychological functions of all participating patients and because the main interest of this study was cognitive functioning and QoL after one year, not all participants were invited for a neuropsychological assessment at Time 2. However, all patients received the questionnaires concerning the psychological variables and QoL at Time 2. The omission of the neuropsychological assessment at Time 2 happened chronologically, so it is unlikely that there is a bias concerning the patients who participated in all three measurement moments versus the patients who participated at Times 1 and 3.

Considerations regarding the analyses

Analyses with neuropsychological measures

In this thesis, standardized scores of the neuropsychological assessments based on the mean and standard deviation of included control group (BBD patients), were used in the analyses. These standardized scores, instead of raw neuropsychological scores (with different ranges in the scoring), were chosen because these scores were summed up to constitute cognitive domain scores.

In Chapter 5 the analyses concerning OCF were done on cognitive domains as well as on each neuropsychological test from the significant cognitive domains in order to present the findings as completely as possible. In the other studies, domain scores of neuropsychological functioning were used in order to limit the number of analyses (and reduce the chance of a Type 1 error and in order to keep the results interpretable.

In the existing literature, the definitions of problems with OCD are inconsistent across studies. Impairment is defined as one, 1.5 and two standard deviation below the mean on one to four tests. Furthermore, a z-score more than one standard deviation below the mean or performance below the 5^{th} or 10^{th} percentile are other definitions used [29]. These different definitions of cognitive impairment in combination with different comparison groups leads to different prevalence rates, as clearly demonstrated by Schilder et al. [50]. We have chosen for a definition of one standard deviation below the mean on a test and patients were classified according to the number of tests on which they significantly decreased (no decrease, decrease on one, two or ≥ three tests). Due to a lack of consensus about the definition in the literature, we have chosen for this sensitive definition to be able to generate indications which neuropsychological performance is affected in patients with BC. However, even with this sensitive definition, only the neuropsychological test of verbal fluency for professions turned out to be significant different in de BC group, compared to the BBD group.

Considerations with regard to the sample size

Efforts have been taken to increase the number of participants in this study by including more hospitals. The sample size of this study is comparable to Jim et al. [51], or even

larger than other studies in this field smaller (e.g., [9, 12, 44, 52-55]). The ambition was to include more patients in this study to preserve statistical power.

A number of additional efforts have been taken to preserve statistical power. For instance, the factor analyses and the regression analyses were done on the sample of patients with a breast problem, instead of the BC patients only. In the regression analyses, diagnosis (BC or BBD) was always included to examine this influence on the dependent variable. Furthermore, preliminary (univariate) analyses were done to reduce the number of independent variables in the final regression analyses. A limitation of this procedure is that this may result in a sample-specific selection of variables in the multivariate regression analyses.

The clinical relevance of significant findings

Besides the statistically significant findings of the studies in this thesis, it is important to examine the clinically relevant effects. Concerning the significant decrease in satisfaction with SCF in BC patients, we were able to conclude that this decrease also was of clinical relevance, based on the defined minimal clinical important difference across time in satisfaction with SCF [56]. With regard to the significant results concerning OCF, the clinical relevance of these findings were not immediately obvious because values of the minimal clinical important differences are unknown.

In addition, besides the comparisons between BC and BBD patients, the scores of the BC patients concerning SCF were also compared with a healthy control group, which provided more insight in the level of problems with SCF. It turned out that the scores of SCF stay within the normal range (based on the healthy control groups).

Implications for further research

Most patients who receive chemotherapy typically receive other treatment modalities as well. Besides the examination of the effects of chemotherapy on cognitive functioning, this thesis preliminary examined the effects of surgery (POCD) on cognitive functioning. Furthermore, it is known that other treatment modalities, such as radiation therapy and/or endocrine treatment can affect cognitive functioning as well. To unravel the separate effects of forms and dosages of (neo-) adjuvant chemotherapy, and other (adjuvant) treatment options for BC, larger prospective neuropsychological studies are needed in patients who are qualified to receive chemotherapy only (or a specific form and dosage of chemotherapy), and patients who are qualified to receive other therapies only (e.g., hormone therapy). However, this is not feasible in clinical practice, because most patients receive a combination of treatment modalities nowadays.

Furthermore, a longer follow-up period would be interesting to examine the duration of the cognitive impairment following breast cancer treatment (verbal memory). Most longitudinal research is focusing on the acute phase after chemotherapy up to one or two years post-treatment. There are suggestions that the effects of chemotherapy on

cognitive functioning diminish over time. However, research has also provided evidence of long-term effects up to 20 years after treatment [57].

In addition, the exclusion criteria of the studies in this thesis were based on conditions that may increase the vulnerability to post-treatment cognitive decline, such as a neurological disorder or alcohol abuse. Therefore, patients who were probably at the highest risk for the most severe changes in cognitive performance may have been excluded from this study. As a consequence, the problems concerning cognitive functioning (OCF and/or SCF) may be an underestimation of the impact of chemotherapy on cognitive functioning. Additional research within samples of patients with BC in combination with other characteristics (e.g., alcohol abuse) is needed to address these questions [58].

Additionally, it would be interesting to gather information about the influence of other side effects of chemotherapy and other treatment modalities (e.g., low hemoglobin levels [59, 60], pain in the arm because of the lymph node dissection, problems with for example the porth-o-cath, admission to the hospital because of side effects) on SCF and OCF. The impact of these side effects on cognitive functioning and QoL are understudied.

In this thesis, the predictors of SCF are examined. The predictors of OCF also need to be examined. OCF is affected by an interplay of multiple factors. It is essential to establishing these factors in order to identify women with BC at higher risk for cognitive problems. Moreover, the potential relevance of psychological mechanisms, such as stress and coping style, in cancer patients' experience of problems with OCF needs to be examined [61]. This can have significant implications for patient care, as changes in psychological factors, such as coping style may be achieved with a variety of interventions that psychologists and other behavioral health care providers can use for people living with cancer.

Furthermore, different potential mechanisms for chemotherapy-induced cognitive dysfunction are described in the literature [62-64]: (i) the ability of certain cytotoxic agents of chemotherapy to cross the blood brain barrier, (ii) oxidative stress and DNA damage, (iii) the effects on cerebrovascular integrity due to cardio-toxicity, (iv) chemotherapy-induced brain alterations, (v) and an increased level of pro-inflammatory cytokines. The last years a number of important findings have been done (e.g., [65-68]), but more insight in these potential mechanisms is needed to better understand the chemobrain.

In addition, it needs to be examined in a larger sample size if the patients with a higher age, lower educational level and the lack of having paid work (the latent class found in Chapter 6) are most vulnerable for the development of problems with OCF after chemotherapy for BC.

Finally, it would be useful to have access to nationwide norms of the different neuropsychological tests based on the healthy population. Until now, studies used norm data based on their own generated control group or the reference data provided in the testing manual of the neuropsychological tests (in which a lot of different reference groups are used). Nationwide reference data will be very useful in the detection of problems with OCF in patients with BC.

Implications for clinical practice

Although more research is warranted to unravel the chemobrain, several implications for clinical practice can be provided based on this thesis.

Evidence-based information provision

The information generated in this thesis about the existence, prevalence and course of problems with OCF and SCF facilitate health care professionals to provide evidence-based information to their patients. This information can be provided to all the patients with BC when they are informed about the other side-effects of chemotherapy as well (by their physician or their nurse practitioner). Patients can benefit from this knowledge in preparing themselves for the potential impact of BC treatment on cognitive impairment.

More specifically, patients can be informed that with regard to side-effects of chemotherapy some patients experience problems with their cognitive functioning during and after treatment. The severity of problems with SCF can shortly increase after treatment and the satisfaction with SCF can decrease after ending chemotherapy. These changes are not disproportionate and for most patients the problems with SCF stay within the normal range. With regard to OCF patients can be informed about the possibility to experience problems concerning verbal memory after treatment. These problems are most severe three months after ending chemotherapy and will come almost at their baseline functioning one year after treatment. Furthermore, patients can be informed about the role of psychological factors (especially depressive symptoms and state anxiety) in the experience of SCF.

Screening for cognitive dysfunction?

As mentioned before, it needs to be considered if the standard neuropsychological assessments are sensitive enough to measure subtle dysfunctioning concerning OCF. This implicates that the implementation of neuropsychological assessments on a large scale does not add significant clarifications for the cause and nature of the problems with OCF in (ex-)BC patients and would be cost ineffective. This screening for OCF will not add significant value to the treatment plan of individual BC patients. Cognitive complaints alone do not justify neuropsychological assessments. It should only be used selectively in those patients in whom a suspicion exists about a decline in OCF based on the anamnestic and hetero-anamnestic details and other well known risk factors besides the BC (e.g., age, alcohol abuse).

Earlier research and this thesis found weak associations between OCF and SCF. However, research has shown that SCF can predict OCF at a later stage [69]. However, this research was done in older adults instead of in a population with a disease, in which the mechanisms may be different. Therefore, the predictive value of SCF on future OCF functioning in BC patients needs to be further examined. Consequently, knowledge about the predictive value of SCF for OCF is too unstable to fully implement a screening tool for problems with SCF in BC patients in clinical practice in order to identify the patients who are at risk of developing problems with OCF. Nevertheless, on an individual basis it can be

worthwhile to measure the SCF of a BC patient, eventually combined with a proxy report, when there are indications that the BC patient suffers from the problems with SCF.

Thus, screening for OCF and/or SCF on a large scale in clinical practice is not recommended based on the findings of this thesis and earlier research.

Interventions in clinical practice

A general intervention

OCF and SCF can have an impact on aspects which are related to QoL and, therefore, attention to problems with OCF and SCF within the health care of BC patients is warranted. However, the impact of chemotherapy on OCF and SCF in patients with BC is limited and therefore, interventions should be time- and cost-efficiently. Therefore, participating in a revalidation program such as '*Herstel en Balans*', which is already currently provided in a number of hospitals and revalidation centers in the Netherlands, is recommended. This revalidation program combined interventions for the psychosocial and physical problems after cancer(-treatment). Until more evidence is derived about the effectiveness of specific interventions for problems with OCF/SCF within patients with BC, interventions with broad neuropsychological, psychological, and physical elements (such as '*Herstel en Balans*') offer the best option for BC patients with problems with OCF.

Interventions for persisting problems with subjective and/or objective cognitive functioning

When problems with SCF/OCF persist in patients after they have followed '*Herstel en Balans*', interventions on an individual basis are recommended. Nowadays, research is focusing on specific, behavioral interventions, pharmacological interventions, and physical activity interventions for patients with cancer and problems with OCF/SCF.

There is evidence for an association between problems with SCF and anxiety, depression, psychological distress, and fatigue. Interventions that have the potential to improve this emotional distress may be partially valuable since cognitive functioning and emotional distress seem to be related. Cognitive behavioral therapy can also be a useful intervention for problems with SCF, as demonstrated in patients with a chronic fatigue syndrome or multiple sclerosis. Their level of fatigue/depression *and* their problems with SCF decreased after treatment with cognitive behavioral therapy [70, 71].

Interventions for individuals with persisting problems with SCF/OCF should rely on the basics, such as stress-management or psycho-education about possible problems with cognitive functioning (OCF and/or SCF) during and after BC treatment with chemotherapy [72]. Cognitive rehabilitation, in which psycho-education is an important element, aims to treat or to teach to manage the cognitive deficits. This can be a useful tool for BC patients. Strategy trainings are used to teach patients to apply strategies to cope with their cognitive problems (e.g., preventing or minimizing distractions, anticipating and planning, pacing of cognitive activities, basic cognitive compensation strategies, and/or use of mnemonics) [73]. Furthermore, retraining of specific cognitive skills can be attempted by means of having patients frequently perform exercises [73]. A number of studies have been done to examine the efficacy of neuropsychological training programs/rehabilitation

programs in cancer patients. Ferguson et al. found an intervention effect for verbal memory [74].

Although pharmacological interventions are available for cognitive problems (see for overviews [73, 75, 76]), this treatment option is not recommended because the chemotherapy-induced cognitive problems are mild and only appear in a subgroup which is not yet clear enough to specify. This would lead to an over-treatment of a patient population that already receives a lot of pharmacological interventions.

Thus, until more evidence is gathered about the effectiveness and the time- and cost efficiency of specific rehabilitation programs as well as cognitive behavioral therapy, patients are recommend to participate in the broad revalidation program '*Herstel en Balans*'. In individuals with persisting problems with SCF/OCF the presence of psychological distress, such as depressive symptoms or state anxiety, must be examined. Interventions aiming at treatment of psychological distress can have a beneficial effect on problems with SCF/OCF. In addition to this intervention, psychologists can make use of cognitive-rehabilitation.

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Appendix

Cognitief functioneren na behandeling voor borstkanker

Lockefeer J

Pullens MJJ

De Vries J

Tijdschrift voor Neuropsychologie. 2010; 5(2):20-28

Samenvatting

Subjective cognitive functioning

Een aanzienlijk deel van de patiënten ervaart subjectieve cognitieve klachten na de behandeling van borstkanker. Echter, slechts bij een klein deel van deze patiënten worden cognitieve stoornissen geobjectiveerd. Factoren zoals angst, depressie en vermoeidheid spelen een belangrijke rol in het subjectief cognitief functioneren. Meer longitudinaal onderzoek met een grote patiëntengroep, controlegroep, gevalideerd test-instrumentarium en normering is nodig om de incidentie en aard van cognitieve achteruitgang, zowel objectief als subjectief na chemotherapie in beeld te brengen. Aandacht voor cognitieve klachten en stoornissen na behandeling van kanker is een belangrijk aandachtspunt tijdens de revalidatie. Psycho-educatie, dagstructurering, stressmanagement en het aanleren van een aantal compensatiestrategieën zijn belangrijke ingrediënten.

Voorwoord

De casusbeschrijving “Cognitieve Problemen na radiotherapie en chemotherapie; niet altijd verwacht” van collegae A. Visser-Meily en C. van Heugten in het Tijdschrift voor Neuropsychologie 2009 nr. 3 [1], inspireerde tot het schrijven van een theoretisch artikel over het cognitief functioneren van borstkankerpatiënten na behandeling met chirurgie en adjuvante (aanvullende) therapie in de vorm van chemotherapie en radiotherapie.

In de betreffende casusbeschrijving heeft patiënte behandeling van een cervixcarcinoom ondergaan met chemotherapie en lokale radiotherapie. Later krijgt zij naast lichamelijke problemen ook klachten van vermoeidheid en cognitie, vooral ten aanzien van het concentratievermogen, het denktempo en de woordvinding. Vanuit beeldvormend onderzoek blijkt er echter geen sprake te zijn van hersenmetastasen. In de theoretische discussie wordt vervolgens wel relatief veel aandacht besteed aan de gevolgen voor het cognitief functioneren van een hersentumor of hersenmetastasen en de behandeling daarvan, terwijl daar bij patiënte toch geen sprake van is. De collegae lijken verbaasd, maar bij patiënten met kanker, die zoals hier adjuvante chemotherapie hebben gehad, komen de genoemde cognitieve problemen veel voor. In de beschrijving van de gevolgen voor het cognitief functioneren van behandeling van kanker met chemotherapie missen wij een aantal relevante aspecten.

Veranderingen in het cognitief functioneren zijn het meest onderzocht bij borstkankerpatiënten, maar zijn ook geconstateerd bij patiënten met andere vormen van kanker die zich niet in het centraal zenuwstelsel (CZS) bevinden, zoals longkanker en lymfeklierkanker [2]. Hieronder geven wij een overzicht van de huidige stand van zaken op dit onderzoeksgebied met betrekking tot borstkanker en doen wij enkele tentatieve uitspraken over de benadering van de cognitieve problematiek die borstkankerpatiënten tijdens en na hun behandeling ervaren.

Inleiding

Borstkanker is een steeds meer voorkomende ziekte in de Verenigde Staten en West-Europa. De verwachting is dat over enkele jaren één op de zeven vrouwen in Nederland borstkanker zal ontwikkelen [3]. De overlevingskans na kanker is door vroege diagnostiek en verbetering van de behandeling sterk toegenomen. Steeds meer vrouwen leven met de lange termijneffecten van kanker, waardoor de kwaliteit van leven sterk in de belangstelling is komen te staan. In de afgelopen tien jaar is er dan ook in toenemende mate onderzoek verricht naar de effecten van chemotherapie op bijvoorbeeld angst, depressie, moeheid en haarverlies [4]. Naast deze lichamelijke en psychische gevolgen van chemotherapie geven meerdere vrouwen aan zich ook zorgen te maken over de consequenties voor het cognitief functioneren van de chemotherapie tijdens en na de behandeling, beter bekend als het ‘chemobrein’. Naar aanleiding van deze zorgen is er veel onderzoek verricht naar cognitieve stoornissen en klachten na behandeling voor borstkanker. Vanwege een recente herziening van de Europese behandelrichtlijn per

september 2008 krijgt vrijwel iedere borstkankerpatiënt na chirurgie adjuvante chemotherapie [5]. De relevantie van deze onderzoeken naar de consequenties van chemotherapie is dus erg groot.

Cognitieve stoornissen en subjectieve cognitieve klachten

Allereerst is het belangrijk om onderscheid te maken tussen cognitieve stoornissen en subjectieve cognitieve klachten. Cognitieve stoornissen zijn te objectiveren door middel van neuropsychologisch onderzoek, terwijl subjectieve cognitieve klachten refereren naar de door de patiënt ervaren cognitieve problemen, en hun tevredenheid met hun cognitief functioneren in het dagelijks leven. Studies naar het cognitief functioneren bij borstkankerpatiënten die naast cognitieve stoornissen ook subjectieve klachten hebben onderzocht, vermelden dat er geen correlaties zijn tussen de objectieve afwijkingen in het neuropsychologisch onderzoek en de zelfrapportage van cognitieve klachten [6, 7]. Er zou wel een verband aanwezig zijn tussen subjectieve cognitieve klachten enerzijds en angst, depressie, vermoeidheid en slechtere gezondheidstoestand anderzijds [8, 9].

Cognitieve stoornissen en subjectieve cognitieve klachten na behandeling voor borstkanker

Bevindingen vanuit studies naar objectief cognitief functioneren

In het verleden werden dikwijls cross-sectionele designs gebruikt om de cognitieve gevolgen van kanker en de behandeling hiervan te onderzoeken. Deze cross-sectionele onderzoeken laten inconsistente resultaten zien in relatie tot de vraag of chemotherapie het brein beïnvloedt. De studie van Wieneke en Dienst was de eerste studie waarbij neuropsychologische testen werden afgenomen bij borstkankerpatiënten (N = 28) met als doel het effect van chemotherapie op het cognitief functioneren te onderzoeken [10]. Uit hun resultaten bleek dat 75% van de patiënten een stoornis had op minimaal één van de testen. Ook andere onderzoekers bevestigden opnieuw dat chemotherapie een negatieve invloed heeft op cognitief functioneren [8, 11, 12]. Verder zou een hogere dosis chemotherapie tot meer cognitieve stoornissen leiden dan een lagere dosis chemotherapie [6, 11]. De aard van de cognitieve stoornissen kent een breed spectrum, inclusief aandacht, snelheid van informatieverwerking, mentale flexibiliteit, werk-geheugen, korte en lange termijn geheugen, visueel geheugen, taal, visueel-ruimtelijke vaardigheden en motorische functies [10-13]. Er zijn echter ook recentere cross-sectionele onderzoeken die geen significante verschillen vinden in cognitief functioneren tussen patiënten die wel en niet behandeld zijn met chemotherapie [14, 15].

Vanwege de uiteenlopende resultaten in de cross-sectionele onderzoeken zijn er in de afgelopen jaren verschillende prospectieve onderzoeken uitgevoerd om de relatie tussen chemotherapie en het brein te onderzoeken. De resultaten van deze onderzoeken lopen, net als bij de cross-sectionele onderzoeken, sterk uiteen. Er zijn studies die een

subtiele achteruitgang rapporteren in veel verschillende domeinen bij borstkanker patiënten na chemotherapie [16-19] maar er zijn ook prospectieve studies die geen achteruitgang vinden [20, 21]. De achteruitgang wordt bij deze studies op verschillende manieren berekend en gedefinieerd: er worden veranderingen op groepsniveau over de tijd bestudeerd [17, 19], er worden verschilscores tussen de twee meetmomenten berekend om vervolgens na te gaan of deze buiten het gecalculeerde reliable change interval vallen [16, 20, 21], of er wordt gebruik gemaakt van een op regressie gebaseerde benadering [18, 19]. Ook de periode waarover het cognitief functioneren wordt bestudeerd loopt uiteen van een moment *tijdens* de chemotherapie [21] tot een jaar *na afronding* van de chemotherapie [16-18, 20].

Momenteel is het inzicht in de effecten van kanker en de behandeling hiervan op cognitief functioneren ontoereikend. Het is van belang om te onderzoeken welk profiel van cognitieve stoornissen naar voren komt en na te gaan wat de kenmerken zijn van de patiënten die cognitieve achteruitgang laten zien op neuropsychologische testen.

Bevindingen vanuit studies naar subjectief cognitief functioneren

Naast deze onderzoeken naar cognitieve stoornissen, zijn er ook studies verricht waarbij de effecten van behandeling op het subjectief cognitief functioneren zijn onderzocht. De prevalentie van subjectieve cognitieve klachten varieert sterk (21-90%), wat mogelijk een gevolg is van de verschillende gehanteerde definities, vragenlijsten en afkappunten [9]. Subjectieve cognitieve klachten komen voor bij borstkankerpatiënten, maar het is niet duidelijk of zij deze vaker ervaren vergeleken met de algemene populatie [22]. Er is geen effect van chemotherapie op de aanwezigheid van subjectieve cognitieve klachten; zowel vóór als na de behandeling worden deze klachten even vaak gerapporteerd. De ernst van de klachten neemt echter wel toe kort na de therapie [7, 23]. Naar het verdere verloop is tot nu toe te weinig gedegen onderzoek gedaan. Momenteel is het nog onduidelijk of de subjectieve cognitieve klachten vóór de behandeling gerelateerd kunnen zijn aan de stress die gepaard gaat met de diagnose borstkanker, of dat subjectieve cognitieve klachten een algemeen symptoom vormen dat in de gehele populatie voorkomt en dus niet specifiek is voor borstkankerpatiënten [9].

Toekomstig onderzoek

Methodologische beperkingen en heterogeniteit van de verschillende bestaande studies maken het moeilijk om definitieve conclusies te trekken. Een cross-sectioneel design maakt het onmogelijk om uitspraken te doen over de causaliteit van cognitieve stoornissen en subjectieve cognitieve klachten. Eveneens maakt het ontbreken van een baselinemeting het moeilijk om te beoordelen of de objectieve of subjectieve cognitieve klachten werkelijk toenemen na de behandeling van borstkanker. Dit is noodzakelijk om te weten omdat bekend is dat al voor de start van de adjuvante therapie cognitieve stoornissen aanwezig kunnen zijn [23, 24]. Andere veel voorkomende beperkingen in bestaande studies zijn de kleine patiëntenpopulaties, de vele verschillende soorten van adjuvante therapie en de gebruikte dosis, het gemis aan controlegroepen en de ontbrekende controle voor verstorende variabelen die van invloed kunnen zijn op de

relatie. Er bestaat een grote diversiteit in de hantering van normen, de meetmomenten en de statistische analyse. Daarnaast kennen bestaande studies veel heterogeniteit in het testinstrumentarium dat gebruikt wordt om een bepaald domein van het cognitief functioneren in kaart te brengen. De inconsistente hantering van de definities die gebruikt worden om cognitief disfunctioneren te definiëren maakt het ook moeilijk om deze studies te evalueren.

In 2006 is een internationale workshop gehouden over onderzoek naar cognitieve stoornissen na chemotherapie, waarbij onder andere werd gepleit voor het opzetten van prospectieve longitudinale studies om de incidentie van cognitieve achteruitgang na chemotherapie beter te kwantificeren [25]. Daarbij werd het belangrijk geacht dat het onderzoek een baselinemeting heeft, dat er grotere onderzoeksgroepen dan tot nu in onderzoek betrokken worden en dat er een controlegroep betrokken wordt. Noodzakelijk hierbij is dat er gevalideerde instrumenten en afkappunten gebruikt worden om objectieve en subjectieve cognitieve klachten te meten. Relevant is daarbij ook dat de gebruikte definitie voor cognitieve achteruitgang duidelijk vermeld wordt, omdat hier namelijk geen 'gouden standaard' voor is. In de beschrijving is het belangrijk om de volgende informatie te geven: het percentage van patiënten dat één of twee standaarddeviaties achteruit is gegaan tussen de baselinemeting en de vervolgmeting, het aantal testen waarin achteruitgang is opgetreden, het aantal cognitieve domeinen dat betrokken is bij de achteruitgang en het percentage van patiënten dat juist verbetert in de loop van de tijd [26]. Vanwege de relatie met subjectieve cognitieve klachten zijn angst, depressieve symptomen, vermoeidheid en kwaliteit van leven verder belangrijke factoren die meegenomen moeten worden in onderzoek.

Momenteel wordt er verder onderzoek gedaan aan de Universiteit van Tilburg. Het primaire doel van dit onderzoek is om die vrouwen met borstkanker te identificeren die een jaar na chemotherapie nog uitgesproken subjectieve en/of objectieve cognitieve stoornissen ervaren, om vervolgens de factoren te vinden die tot het cognitieve disfunctioneren bijdragen en tenslotte te onderzoeken hoe groot de invloed van cognitief disfunctioneren is op de kwaliteit van leven van deze vrouwen. In samenwerking met het Center of Research on Psychology in Somatic Diseases van de Universiteit van Tilburg wordt in het TweeSteden ziekenhuis in Tilburg specifiek onderzocht of het niveau van subjectieve cognitieve klachten tot een jaar na de behandeling van borstkanker te voorspellen is vanuit een stress-kwetsbaarheidsmodel en of hiervoor andere risicofactoren te identificeren zijn.

Mechanismen die een rol kunnen spelen in cognitief disfunctioneren na chemotherapie

In een review van Vardy en Tannock wordt een overzicht gegeven van mogelijke mechanismen die een rol kunnen spelen in de ontwikkeling van cognitieve stoornissen bij chemotherapie [2]. Vardy en Tannock stellen dat de etiologie van cognitieve stoornissen nog onbekend is, maar waarschijnlijk multifactorieel bepaald is [2]. Mogelijke

mechanismen betreffen directe neurotoxische effecten zoals schade aan neuronen of omringende cellen en veranderingen in niveaus van neurotransmitters. Ondanks dat het brein een beschermingmechanisme heeft via de bloed-hersenbarrière, blijkt dat chemotherapeutica toch toegang krijgen tot de hersenen. Daarnaast zijn er indirecte effecten zoals hormonale veranderingen, ontregeling van het immuunsysteem, bloedstolsels in kleine vaten van het CZS en anemie.

Beeldvormend onderzoek toont aan dat bij ex-kankerpatiënten die behandeld zijn met chemotherapie een afname van grijze en witte stof optreedt. Ook blijkt dat patiënten na behandeling met chemotherapie, bij de uitvoering van geheugentaken een verhoogde activering hebben in andere hersengebieden (bijvoorbeeld het cingulaire gebied, de gyrus frontalis inferior van de prefrontale cortex en cerebellum posterior) dan gezonde controleproefpersonen. Het brein werkt blijkbaar anders tijdens en na chemotherapie, maar de relatie met cognitieve stoornissen zoals geobjectiveerd in neuropsychologisch onderzoek is onduidelijk. Ook in neurofysiologische studies, waarin veranderingen in Event Related Potential en EEG's zijn aangetoond, worden geen correlaties gevonden tussen resultaten in neuropsychologisch onderzoek en neurofysiologische maten.

Veel kankerpatiënten krijgen een gecombineerde behandeling bestaande uit chirurgie (met variaties in uitgebreidheid en anesthesie), radiotherapie en hormoontherapie. Ook gebruiken de meeste kankerpatiënten pijnstillers en anti-emetica, middelen om misselijkheid en braken tijdens chemotherapie tegen te gaan. Van al deze middelen is nog onvoldoende bekend in hoeverre ze het cognitief functioneren nadelig beïnvloeden. Ook na behandeling met chirurgie en radiotherapie zonder adjuvante chemotherapie kunnen cognitieve stoornissen optreden [14]. Jim e.a. vonden geen verschillen tussen patiënten die na chirurgie behandeld werden met alleen chemotherapie, een combinatie van chemotherapie en radiotherapie of alleen radiotherapie [27]. De gevonden cognitieve stoornissen waren subtiel en lijken meer het resultaat van algemene effecten van kanker en de behandeling daarvan dan het resultaat van alleen chemotherapie [2].

Implicaties voor interventies ten aanzien van subjectieve cognitieve klachten en cognitieve stoornissen

Uit de voorafgaande beschouwing blijkt dat een meerderheid van de patiënten subjectieve cognitieve klachten rapporteert die niet objectiveerbaar zijn door middel van neuropsychologisch onderzoek. Hoewel het mogelijk is dat neuropsychologische testen niet sensitief genoeg zijn om subtiele cognitieve stoornissen in kaart te brengen valt het niet te ontkennen dat subjectieve cognitieve klachten in hoge mate samenhangen met vermoeidheid en psychologische factoren zoals angst en depressie. Dit impliceert dat het op grote schaal toepassen van neuropsychologische diagnostiek in de klinische praktijk vooralsnog weinig zou kunnen toevoegen aan het verhelderen van de oorzaak en de aard van het cognitief disfunctioneren bij (ex-)kankerpatiënten en zeer kostenineffectief zal zijn. Voor het opstellen van een behandelplan heeft het dan een geringe toegevoegde

waarde. Cognitieve klachten rechtvaardigen naar onze mening dus niet zonder meer neuropsychologische diagnostiek zoals Visser-Meily en van Heugten in hun casuïstiek stellen [1]. Uitgebreide neuropsychologische diagnostiek zou dan ook voorlopig selectief kunnen worden ingezet bij die patiënten bij wie op basis van de anamnestische en hetero-anamnestische gegevens en bekende risicofactoren (zoals leeftijd, overmatig alcoholgebruik, familiaire belasting et cetera) een verdenking bestaat op een te objectiveren achteruitgang in het cognitief functioneren.

Desondanks zijn cognitieve stoornissen en klachten zeer bepalend voor de kwaliteit van leven [28] en is het van belang dat er aandacht aan wordt besteed binnen het zorgaanbod voor de oncologische patiënt. Omdat moeheid en stemmingsproblemen vaak nog lange tijd na de behandeling voor kanker aanwezig zijn en een samenhang vertonen met subjectieve cognitieve klachten [9] zijn basisinterventies zoals psycho-educatie over mogelijke cognitieve problemen na behandeling voor kanker, dagstructurering, stressmanagement en eerste stap interventies zoals opgenomen in de recent gereviseerde richtlijn voor de behandeling van depressie het meest aangewezen. Hier zou het leren toepassen van een aantal basale cognitieve compensatiestrategieën aan toegevoegd kunnen worden. Dit is een vorm van zorgaanbod die prima kan plaatsvinden in de eerste en tweede lijn. Ook het programma Herstel en Balans zoals dat in diverse ziekenhuizen en revalidatiecentra wordt aangeboden, omvat een groot aantal van deze elementen [29].

In de beschreven casus van Visser-Meily en van Heugten [1] lijken de hierboven beschreven aspecten van behandeling eveneens een belangrijke rol te hebben gespeeld. Door de aangeboden structuur ervaart patiënte minder druk en vermoeidheid en blijkbaar ook minder cognitieve klachten. Dit ligt in de lijn van de resultaten van een studie bij patiënten met het chronisch vermoeidheidssyndroom [30], waaruit bleek dat zowel het niveau van vermoeidheid als van subjectieve cognitieve klachten significant daalde na behandeling met cognitieve gedragstherapie. Het is dan ook in de casus van Visser-Meily en van Heugten [1] de vraag of vermoeidheid en stemming niet een prominentere rol hebben gespeeld in het cognitief functioneren dan aanvankelijk werd aangenomen.

Omdat een aanzienlijk deel van deze patiënten last heeft van cognitieve klachten, welke een hoge correlatie hebben met angst en depressie, is het wel degelijk noodzakelijk dat “verwerkingsproblematiek” na een ernstige ziekte zoals kanker een centrale plek in de behandeling krijgt. De ziekte kanker grijpt diep in het persoonlijk leven in en raakt aan alle levensgebieden. Dit wil echter niet zeggen dat er aan cognitieve klachten en stoornissen voorbij kan worden gegaan. Het verdient dan ook zeker aanbeveling om psycho-educatie en het aanleren van compensatiestrategieën in een uitgebreider behandeltraject op te nemen.

Conclusie

Een deel van de borstkankerpatiënten houdt cognitieve klachten na de behandeling van kanker. Het is van belang om onderscheid te maken tussen cognitieve stoornissen en subjectief cognitief functioneren in de praktijk. Deze klachten en/of stoornissen zijn over

het algemeen subtiel, maar kunnen langdurig aanwezig zijn en een negatieve invloed op de kwaliteit van leven uitoefenen. Verschillende mechanismen kunnen direct of indirect leiden tot cognitieve stoornissen door chemotherapie. De subjectieve klachten hebben een verband met angst, depressie en vermoeidheid. Grote longitudinale studies met een baselinemeting, een adequate controlegroep en een gevalideerd testinstrumentarium zijn noodzakelijk om de risicogroep en het profiel van cognitieve stoornissen preciezer in kaart te brengen. Wij onderschrijven het belang van aandacht voor de cognitieve problematiek in de revalidatie na behandeling voor kanker en pleiten voor het uitvoeren van effectstudies op dit terrein.

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Nederlandse samenvatting

Chemotherapie is naast radiotherapie en chirurgie een veel gebruikte behandeling voor borstkanker. Het verbetert de levensverwachting van vrouwen met borstkanker aanzienlijk, maar het gaat ook gepaard met verschillende bijwerkingen. Onder deze bijwerkingen vallen onder andere de problemen met het cognitief functioneren. Aan deze bijwerking is de laatste jaren in toenemende mate aandacht besteed. Dit proefschrift beschrijft een prospectief onderzoek naar cognitief functioneren (zowel subjectief cognitief functioneren (SCF) als objectief cognitief functioneren (OCF)) en kwaliteit van leven bij vrouwen met borstkanker. Hiervoor hebben we bij vrouwen met borstkanker die daarvoor behandeld (gaan) worden met chemotherapie en bij vrouwen met een benigne afwijking aan de borst (controlegroep) op drie meetmomenten verschillende cognitieve functies bestudeerd en hebben we verschillende psychologische variabelen onderzocht.

Subjectief cognitief functioneren

In **hoofdstuk 2** is een kritisch overzicht gegeven van de reeds gepubliceerde onderzoeken naar SCF bij vrouwen met borstkanker die daarvoor onder andere zijn behandeld met chemotherapie. Hieruit bleek dat de prevalentie van problemen met SCF aanzienlijk varieert. Mogelijke verklaringen hiervoor zijn de verschillende definities, vragenlijsten en afkappunten die gebruikt zijn om SCF te meten. Verder vonden we dat problemen met SCF inderdaad voorkomen bij vrouwen met borstkanker, maar het is onbekend of deze problemen bij hen vaker voorkomen dan in de algemene populatie. De literatuur liet geen verschillen zien in de prevalentie van problemen met SCF *voor* en *na* de behandeling voor borstkanker, wat indiceert dat er geen effect is van de behandeling op het voorkomen van de problemen met SCF. Ten opzichte van een baseline meting (*voor* de behandeling met systemische therapie) was er desondanks wel bewijs gevonden voor een toegenomen *ernst* van de problemen met SCF op korte termijn na de systemische behandeling. Verder is er in dit review een sterk bewijs voor het gebrek aan een relatie tussen SCF en OCF gevonden (beide globaal gemeten).

Een andere bevinding uit hoofdstuk 2 was dat de manier waarop problemen met SCF gemeten is inconsistent is tussen de studies. Verschillende ad-hoc semigestructureerde interviews en meerdere zelfrapportage vragenlijsten zijn hiervoor gebruikt. Eén van de gebruikte vragenlijsten is de Cognitive Failures Questionnaire (CFQ). Omdat hiervoor meerdere factorstructuren bekend zijn in verschillende patiënten populaties was het doel van **hoofdstuk 3** om de psychometrische eigenschappen van de vragenlijst bij vrouwen met een probleem aan de borst te onderzoeken. Geen van de bestaande modellen paste goed in onze sample zoals bleek uit confirmatieve factoranalyses. Uit een exploratieve factor analyse is gebleken dat een structuur met drie factoren (Vergeetachtigheid, Afwezigheid en Sociale roekeloosheid) goede psychometrische eigenschappen heeft. Hiermee zou de *frequentie* van problemen met SCF bij vrouwen met een probleem aan de borst goed gemeten kunnen worden.

In hoofdstuk 2 zijn verder nog tekortkomingen van de gedane studies naar problemen met SCF beschreven: het cross-sectionele karakter van vele studies beperkt de

conclusies met betrekking tot causaliteit en de ontwikkeling van problemen met SCF over de tijd. Daar komt bij dat het gebrek aan een baseline meting het onmogelijk maakt om te beoordelen of er ook daadwerkelijk sprake is van een toename in de problemen met SCF na behandeling met systemische behandeling. Andere tekortkomingen omvatten onder andere de kleine groepen waarin het onderzoek is gedaan, het gebrek aan een controle groep en het gebrek aan controle voor variabelen die mogelijk ook een invloed hebben op de relatie (confounding variabelen). Daarom beschreef **hoofdstuk 4** van dit proefschrift een prospectieve studie met een controle groep en een meting op baseline naar de problemen met SCF bij vrouwen met borstkanker die daarvoor behandeld (gaan) worden met chemotherapie. Hierbij was zowel de *tevredenheid* met het SCF als de *frequentie* van de problemen met SCF gemeten *voor* de start met de chemotherapie en drie maanden *na* de laatste kuur. Deze analyses zijn op twee manieren gedaan: de ene keer zonder rekening te houden met verstorende variabelen en vervolgens nog een keer met daarin verschillende variabelen als covariaten. Naast de geïncludeerde controlegroep hebben we de problemen met SCF ook nog kunnen vergelijken met een normpopulatie. Vrouwen met borstkanker verschilden niet in de *frequentie* van de problemen met SCF vergeleken met vrouwen met een benigne afwijking aan de borst, maar de *tevredenheid* met het SCF was wel afgenomen drie maanden na de laatste chemotherapie. Deze daling in de *tevredenheid* met SCF is ook klinisch relevant bevonden. Op beide meetmomenten bleven de gemiddelde scores van de *tevredenheid* met SCF echter wel binnen de normale range van scores (gebaseerd op de normpopulatie). Verder hebben we in dit onderzoek gevonden dat psychologische factoren (met name depressieve symptomen en situationele angst) voorspellers zijn voor de *frequentie* van problemen met SCF. Psychologische factoren, diagnose (maligne/benigne) en een eerdere behandeling door een psycholoog/psychiater bleken voorspellers te zijn voor de *tevredenheid* met SCF.

Met betrekking tot SCF kan dus geconcludeerd worden dat de *ernst* van problemen met SCF op korte termijn toeneemt na de behandeling. De *tevredenheid* met SCF was afgenomen drie maanden na de laatste chemotherapie. Ondanks het feit dat de problemen binnen de range van de normpopulatie bleven, moet de statistische en klinisch relevante afname in *tevredenheid* met SCF serieus genomen worden.

Objectief cognitief functioneren

In **hoofdstuk 5** was het effect van chemotherapie op OCF (de verschillende domeinen als ook op de verschillende neuropsychologische testen) in vrouwen met borstkanker onderzocht door vergelijkingen te maken met vrouwen met een benigne afwijking aan de borst *voor* en drie maanden *na* het beëindigen van de chemotherapie (en op vergelijkbare momenten gemeten bij de groep vrouwen met een benigne afwijking aan de borst). Vrouwen met borstkanker lieten een aangetast verbaal geheugen zien over de tijd vergeleken met vrouwen met een benigne afwijking aan de borst. Met betrekking tot het executief functioneren waren er wisselende resultaten gevonden: de verschillende neuropsychologische testen lieten geen significante verschillen zien met betrekking tot de

effecten van tijd of groep, maar de gecreëerde domeinscore liet een significant interactie effect zien (waarbij vrouwen met borstkanker drie maanden na de laatste chemotherapie verslechterd waren terwijl de vrouwen met een benigne afwijking aan de borst een kleine verbetering in het executief functioneren lieten zien). Verder vonden we alleen op de test voor de verbale vlotheid met betrekking tot beroepen een verschil tussen de vrouwen met borstkanker en vrouwen met een benigne afwijking aan de borst in het percentage van patiënten die een verbetering of een verslechtering lieten zien op de neuropsychologische testen. Vervolgens hebben we de resultaten met betrekking tot het OCF ook geanalyseerd met behulp van de 'Reliable Change Index' die gecorrigeerd was voor leereffecten. Hiermee kunnen individuen met een significante verandering over de tijd geïdentificeerd worden. We hebben geen verschillen gevonden in sociodemografische en psychologische variabelen tussen patiënten die een achteruitgang lieten zien op drie of meer neuropsychologische testen en patiënten met een achteruitgang op twee of minder neuropsychologische testen. In dit hoofdstuk hebben we verder nog kleine tot matige correlaties tussen specifieke neuropsychologische testen en de specifieke factor Sociale roekeloosheid van de CFQ gevonden.

Het doel van **hoofdstuk 6** was om het verloop van OCF tot één jaar na de afronding van de chemotherapie bij vrouwen met borstkanker te vergelijken met vrouwen met een benigne afwijking aan de borst. Het verbale geheugen van de vrouwen met borstkanker was afgenomen een jaar na de laatste chemotherapie, terwijl het verbale geheugen van de vrouwen met een benigne afwijking aan de borst stabiel bleef over de tijd. Daarnaast hebben we in hoofdstuk 6 het bestaan van verschillende longitudinale trajecten in de groep vrouwen met borstkanker onderzocht. Latente klasse analyses lieten drie klassen van vrouwen met borstkanker zien: 'consistent hoog cognitief functioneren', 'consistent gemiddeld cognitief functioneren' en 'consistent laag cognitief functioneren'. Vrouwen met borstkanker in deze laatste groep waren significant ouder, minder goed opgeleid en hadden vaker geen betaald werk (of zijn met pensioen). De mogelijke kwetsbaarheid van deze groep met minder cognitieve reserve moet verder onderzocht worden.

Invloed van cognitief functioneren op kwaliteit van leven

Om beter inzicht te krijgen in de relatieve invloed van cognitief functioneren op de gesteldheid van vrouwen met borstkanker hebben we in **hoofdstuk 7** de unieke bijdrage van cognitief functioneren (SCF en OCF) aan de kwaliteit van leven onderzocht. Vergeleken met vrouwen met een benigne probleem aan de borst bleek dat de totale kwaliteit van leven en algemene gezondheid en het domein van fysieke gezondheid aangedaan waren een jaar na de laatste chemotherapie bij vrouwen met borstkanker. Cognitief functioneren (SCF en OCF) bleek geen significante variantie toe te voegen aan het voorspellende model voor kwaliteit van leven (gecontroleerd voor sociodemografische, medische en psychologische variabelen). In de praktijk blijven vrouwen met borstkanker echter wel aangeven dat ze gehinderd worden door de cognitieve veranderingen tijdens en na de behandeling voor borstkanker. Meer onderzoek naar deze relatie is dus nodig.

Implicaties voor de praktijk

De bevindingen van dit onderzoek over het bestaan, de prevalentie en de ontwikkeling van problemen met SCF en OCF kunnen clinici ondersteunen in het verschaffen van 'evidence-based' informatie. Ze kunnen patiënten uitleggen dat sommige patiënten problemen ervaren met het cognitief functioneren tijdens en na de behandeling met chemotherapie. De *ernst* van de problemen met SCF kan tijdelijk toenemen na de behandeling en de *tevredenheid* met SCF kan afnemen nadat de chemotherapie afgerond is. Deze veranderingen zijn echter niet buiten proportioneel, bij de meeste patiënten blijven de problemen met SCF binnen de ´normale range´. Met betrekking tot het OCF kunnen patiënten geïnformeerd worden over de mogelijke problemen in het verbale geheugen na de behandeling. Deze problemen zijn het duidelijkst drie maanden na de laatste chemotherapie en het functioneren met betrekking tot het verbale geheugen is een jaar na de laatste chemotherapie weer bijna te vergelijken met het baseline niveau. Verder kunnen patiënten geïnformeerd worden over de rol van psychologische factoren (met name depressieve symptomen en situationele angst) in de ervaringen met betrekking tot SCF. Deze informatie kan patiënten helpen om zich voor te bereiden op de potentiele invloed van de behandeling voor borstkanker of het cognitief functioneren.

Dit proefschrift vindt een beperkte invloed van chemotherapie op het cognitief functioneren bij vrouwen met borstkanker. Om deze reden moeten eventuele interventies tijd- en kosten effectief zijn. Totdat er meer bewijs is over de effectiviteit voor interventies die specifiek ontwikkeld zijn voor problemen met OCF/SCF bij vrouwen met borstkanker, bieden interventies met meerdere elementen (neuropsychologisch, psychosociaal, fysiek) een goede mogelijkheid om vrouwen met borstkanker te helpen met hun problemen met het cognitief functioneren. Het participeren aan het bestaande revalidatieprogramma zoals 'Herstel en Balans' is daarom aanbevolen. In dit revalidatieprogramma worden interventies voor psychosociale en fysieke problemen na (de behandeling van) kanker gecombineerd. Wanneer de problemen met het cognitief functioneren aan blijven houden ondanks dat vrouwen aan bijvoorbeeld 'Herstel en Balans' hebben geparticipeerd, is een interventie op individuele basis aanbevolen. Op dit moment worden er verschillende onderzoeken uitgevoerd naar het effect van specifieke gedragsinterventies, farmacologische interventies en interventies waarbij fysieke activiteit centraal staan op het cognitief functioneren bij patiënten met kanker.

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List of publications

- Pullens MJJ, De Vries J, Van Warmerdam LJC, Van de Wal MAW, Roukema JA. Chemotherapy and subjective cognitive complaints in patients with breast cancer. Psycho-Oncol, 2012, epub ahead of print.

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- Pullens MJJ, De Vries J, Bogaarts MP, Roukema JA. Subjective cognitive functioning in patients with breast problems: the cognitive failures questionnaire. Submitted.

- Pullens MJJ, Roukema JA, Luiten EJT, Van Riel JMGH, De Vries J. Chemotherapy and objective cognitive functioning in patients with breast cancer. Submitted.

- Pullens MJJ, Vermunt JK, Roukema JA, Van Riel JMGH, Roerdink HTJ, De Vries J. Identifying the different courses of cognitive functioning across time in patients with breast cancer treated with chemotherapy. Submitted.

- Pullens MJJ, Roukema JA, Schepers-Van der Sterren EEM, De Vries J. The relationship between cognitive functioning and quality of life in patients with breast cancer who receive chemotherapy. Submitted.

- Abrahams H, Pullens MJJ, Roukema JA, De Vries J. Predictors of multiple domains of objective cognitive functioning. Submitted.

- Pullens MJJ, Heikens JT, Van Mierlo-Jansen P, Bemelman WA, Van Laarhoven CJHM, De Vries J. Development and validation of a questionnaire assessing sexual dysfunction in women after pelvic surgery. Submitted.

- De Zeeuw S, Pullens MJJ, Heikens J, De Vries, J, Bemelman WA, Van Laarhoven CJHM. Experienced sexual dysfunction and quality of life in women after ileo-puch anal anastomis. Submitted.

- Bosma E, Pullens MJJ, De Vries J, Roukema JA. The impact of complications on Quality of Life following colorectal surgery: A prospective cohort study to evaluate the Clavien-Dindo classification system. Submitted.